**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF SOUTH CAROLINA**
**CHARLESTON DIVISION**

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| **IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION** | ) | **MDL No. 2:14-mn-02502-RMG** |
| | ) | **This document relates to:** |
| | ) | **All actions** |

**PFIZER'S MOTION TO EXCLUDE PLAINTIFFS' EXPERT TESTIMONY ON THE ISSUE OF GENERAL CAUSATION AND MEMORANDUM IN SUPPORT**

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Defendant Pfizer Inc. respectfully moves, pursuant to Fed. R. Evid. 104(a), 702, 703, and 403, to exclude expert testimony, including the opinions of John Abramson, M.D., Edwin Gale, M.D., Nicholas Jewell, Ph.D., Michael Quon, M.D., Ph.D., Barbara Roberts, M.D., and Sonal Singh, M.D., M.P.H., that Lipitor causes diabetes or, at minimum, that Lipitor causes diabetes (a) at doses less than 80 mg or (b) in those with less than three of the following risk factors for diabetes: (i) baseline fasting blood glucose above 100 mg/dl, (ii) fasting triglycerides above 150 mg/dl, (iii) Body Mass Index above 30, or (iv) a history of hypertension.

## PRELIMINARY STATEMENT

Plaintiffs' experts claim the science demonstrates that Lipitor (atorvastatin) causes diabetes. This question has been evaluated outside of litigation through controlled clinical trials and meta-analyses of clinical trials, as well as nearly two decades and more than 250 million patient-years of Lipitor use. Of all those clinical trials, *post hoc* analysis of only one, the SPARCL trial, has reported a small increase in new diabetes diagnoses over placebo. That analysis reported an association only in patients who took the 80 mg dose of Lipitor, the highest dose, and only in patients with three or more preexisting risk factors for diabetes. The available data do not provide a scientifically reliable basis for Plaintiffs' experts' leap from a reported association of a slight increase in the diagnosis of diabetes to causation of the disease.

Doing so is contrary to Plaintiffs' experts' admissions on the development of the diabetes disease process and to adjudicated clinical trial data, which Plaintiffs' experts ignore. Their methods for assessing causation are scientifically unreliable. They variously employ litigation-driven standards that ignore undisputed clinical facts about diabetes, rely on their statistically infirm *post hoc* analyses of data from select Lipitor clinical trials, and rely on observational studies that they admit cannot establish causation due to chance, bias, and confounding. Plaintiffs' experts purport to extrapolate, without support, from a limited association of a slight increase in new diabetes diagnoses in patients who took the 80 mg dose of Lipitor and who had

three or more risk factors for diabetes to causation in ***all*** patients and at ***all*** doses of Lipitor. Plaintiffs' general causation experts should be excluded.[1]

Cardiovascular disease is the number one killer of both men and women, and elevated cholesterol is a well-recognized risk factor for cardiovascular disease. Among the cholesterol-lowering medicines known as statins, Lipitor is one of the most efficacious. It is also one of the best-studied and most-prescribed medicines in history. Lipitor is approved to lower LDL cholesterol and prevent heart attacks, strokes, and other cardiovascular events in both men and women. Lipitor is also approved to treat patients with type 2 diabetes who do not have coronary heart disease (CHD) but have its risk factors. Indeed, due to the increased potential cardiovascular risk associated with diabetes, prescription of a statin is the standard of care for patients with diabetes.

As with all prescription medicines, the labeling for Lipitor includes information about certain potential safety risks, some of which can be serious. Since Lipitor was first approved in 1996, FDA has approved the Lipitor labeling more than a dozen times to make certain additions and changes to both efficacy and safety information. This litigation followed after one such labeling change. In 2012, FDA announced a change to the physician-directed prescribing information for Lipitor and multiple other statins to state in the warning section that "[i]ncreases in HbA1c and fasting serum glucose levels" – biological markers used to diagnose diabetes – "have been reported with [statins], including LIPITOR." *See* Ex. 5, 2015 Lipitor Label at 6. This language does not say that Lipitor causes diabetes. Nor has FDA required or requested that Pfizer include any reference to diabetes in the warning section of the Lipitor labeling.

Plaintiffs proffer six experts who together claim that Lipitor is "*causally* linked with type 2 diabetes." Singh Rpt. (Ex. 6) at 40.[2] In doing so, they draw no lines in limiting the scope of

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[1] Beyond issues of general causation, Plaintiffs' experts concede there is no recognized methodology or test capable of establishing specific causation – *i.e.*, that Lipitor caused a particular plaintiff's diabetes. Gale Tr. (Ex. 1) at 57:18-58:17; Quon Tr. (Ex. 2) at 326:18-327:4; Singh Tr. (Ex. 3) at 324:6-325:6; Abramson Tr. (Ex. 4) at 161:6-25. Pfizer will address specific causation issues in case-specific *Daubert* motions.

their opinions, whether to dose or duration, and go so far as to say that even ***one pill*** of 10 mg Lipitor can cause diabetes. *See* Quon Tr. (Ex. 2) at 332:11-21; Singh Tr. (Ex. 3) at 268:9-23. Plaintiffs' medical experts include Dr. Gale, a diabetologist, Dr. Quon, a researcher and internist, Dr. Roberts, a cardiologist who has written a book that advances outlier opinions about statins, and Dr. Abramson, a former family physician who has been a professional plaintiffs' witness for the last decade. Plaintiffs also proffer opinions from Dr. Singh, an internist with a masters degree in public health, and Dr. Jewell, a statistician with no medical training or expertise who appears as a plaintiffs' expert witness in varied pharmaceutical litigations, and whose statistical analyses of Lipitor studies Plaintiffs' medical experts uncritically accept. *See* Gale Tr. (Ex. 1) at 266:23-267:3; Quon Tr. (Ex. 2) at 44:7-12, 196:10-197:4, 300:8-23; Singh Tr. (Ex. 3) at 299:2-24, 313:10-17; Abramson Tr. (Ex. 4) at 160:18-23; Roberts Tr. (Ex. 9) at 141:6-142:11.

The methods used by these experts violate the standards they apply outside the courtroom and are fatally flawed. The patchwork of unsupported assumptions and unreconciled contradictions between and within these experts' opinions reveals them to be unreliable. What Pfizer sets forth below is not an exhaustive chronicle of the pervasive errors in Plaintiffs' experts methodology, but only the most obvious errors. These errors render their opinions inadmissible under *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993), and its progeny.

**Plaintiffs' Experts Disregard Clinical Reality**

Plaintiffs' expert testimony on general causation is inadmissible due to the wide gap between their causation analyses and their admissions concerning the clinical progression of diabetes. To the extent they offer any medical opinions, they do not dispute the key features of the diabetes disease process. They admit that type 2 diabetes is a disease that takes many ***years*** to develop, and is caused by a host of contributory risk factors, the most significant being weight, age, race, and genetics. These admissions are fatal to their attempts to prove general causation.

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[2] *See also* Jewell Tr. (Ex. 7) at 93:9-94:6; Abramson Tr. (Ex. 8) at 483:18-488:16; Gale Tr. (Ex. 1) at 213:20-24; Quon Tr. (Ex. 2) at 24:3-9.

While certain blood glucose thresholds have been established to determine when someone is clinically deemed "diabetic," at the time an individual crosses those thresholds, she will have already had the disease for ***at least a decade***, and have been "prediabetic." Thus, the moment an individual crosses the diagnostic threshold for "diabetes" – over 125 mg/dl is the current diagnostic cut point – is usually more than ten years after the last event that caused the disease process. Plaintiffs' experts generally agree that this threshold is primarily a diagnostic tool and that crossing the threshold does not necessarily signify any clinically significant physiological change from just below 125 mg/dl. Indeed, individuals who are just below 125 mg/dl are not "normal" (rather, those below 100 mg/dl are normal). Those between 100 and 125 mg/dl are "prediabetic," since the decade-long disease process is already underway and puts them well on the road to a diagnosis of "diabetes."

Nor can Plaintiffs' experts cure the clinical contradictions of their general causation opinions by retreating to a fallback position by claiming only that Lipitor causes increases in blood glucose. Just as the magnitude of the alleged risk for newly diagnosed diabetes at 80 mg is slight, so is any increase in blood glucose. One of Plaintiffs' experts states that on average Lipitor increases HbA1c by only 0.1% – or about 2 to 3 mg/dl – an increase in blood glucose that he and others admit is of no clinical concern. Gale Tr. (Ex. 1) at 49:12-50:1, 154:2-9, 205:2-13; Quon Tr. (Ex. 2) at 175:22-176:20. In contrast, HbA1c increases of 0.3 or 0.4%, or perhaps 1.0%, are the threshold for clinical significance. Gale Tr. (Ex. 1) at 50:6-51:5; Quon Tr. (Ex. 2) at 175:22-176:20. Many factors can increase blood glucose, such as weight gain, aging, lack of exercise, and a high carbohydrate diet. Quon Tr. (Ex. 2) at 261:2-11, 270:17-19.

Against this backdrop, Dr. Jewell's analysis of clinical trial data purports to show that Lipitor is statistically associated with an increased risk of individuals crossing the diagnostic threshold for diabetes, an association he erroneously equates with causation. Given the existence of well-established and large risk factors for diabetes compared to the slight blood glucose elevations reported in association with Lipitor, the absence of an association of newly diagnosed diabetes in patients without multiple risk factors for diabetes, and the length of time

that Plaintiffs' clinical experts admit it takes to develop diabetes, any purported association between Lipitor and an increase in diabetes diagnoses in such trials cannot be causal since Lipitor would have been introduced after the decade-long disease process began. Dr. Jewell's statistical analysis cannot show that the subsequent use of a medicine causes a pre-existing disease process.

Dr. Singh likewise errs in his meta-analysis of statin trials, opining that his observed association is causal because "in the majority of cases, the onset of diabetes was relatively shortly after statin exposure (frequently < 4 months)." Singh Rpt. (Ex. 6) at 36. But rapid onset of a diabetes diagnosis precludes causation, since the diabetes disease process started years before, and cannot have been caused by the recent introduction of statins. Newly diagnosed diabetes in patients who were on the verge of a diagnosis as part of the continuing progression of a long-term disease process is neither surprising nor indicative of causation.

Further, the risk that Plaintiffs' experts purport to find from inconsistent clinical trial results, even if real, is small. This slight increase is overwhelmed by other well-recognized risk factors for diabetes, including weight gain, age, ethnicity, genetics, sedentary lifestyle, high blood pressure, high triglycerides, low HDL cholesterol, depression, psychosis, cigarette smoking, and exposure to some environmental toxins. Plaintiffs' experts offer no reliable basis for opining that the small association reported with statin use is causal in light of the role of so many other large, recognized risk factors. In fact, they admit that none of them is aware of any method to determine in an individual patient that Lipitor, as opposed to any number of other risk factors, caused a patient's diabetes, a concession that is both relevant to general causation and fatal to specific causation.

So, too, Dr. Jewell's methods contravene medical knowledge about diabetes. Dr. Jewell is a statistician, not an epidemiologist or a medical doctor. Lacking any medical training or expertise, he divorces any clinical judgment from his statistical analysis. Unsurprisingly, error abounds. For instance, instead of using generally accepted medical definitions, he builds his analysis around individuals he deems to be "without baseline glucose abnormalities," which he

defines to mean anyone below 126 mg/dl. Jewell Rpt. (Ex. 10) at 4 n.1. But by using his private, litigation-only definition, he "cures" all prediabetic individuals with fasting blood glucose levels between 100 and 125 mg/dl – some 86 million American adults[3] – and treats them instead as being normal, introducing a methodological flaw that permeates his analysis. While it does not itself constitute a basic math error, it does evince a lack of understanding of what the math means, and Plaintiffs' attempt to fix this and other errors after his first deposition shows that his litigation opinion is a moving target that should be stricken under *Daubert*.

**Unscientific Methodology**

Beyond issues of clinical incoherence, Plaintiffs' experts' methodology is unscientific. Initially, Dr. Jewell erroneously conflates association and causation, treating the existence of the former as *ipso facto* proof of the latter. As many courts have held, and as Plaintiffs' other experts concede, doing so is unreliable and contrary to fundamental scientific methodology.[4]

Moreover, to test a hypothesized association, a study "needs to be designed with that particular question in mind before the data are collected." Hennekens Rpt. (Ex. 14) at 24; *see* Gale Tr. (Ex. 1) at 244:24-245:25. Yet none of the studies on which Dr. Jewell based his report was designed to test for an association between Lipitor and diabetes. Instead, his initial causation opinion as to diabetes was based almost entirely on his own unpublished *post hoc* litigation analysis of data from one trial, SPARCL. Jewell Tr. (Ex. 7) at 103:13-24. SPARCL was not designed to study whether Lipitor increases the risk of being diagnosed with diabetes and tested only the 80 mg dose of Lipitor.

Though Dr. Jewell has testified elsewhere that a reliable methodology must evaluate the totality of the evidence, his approach here was just the opposite. In performing his analysis, Dr. Jewell intentionally ignored ASCOT, *id.* at 119:11-15, 122:14-25, the sole Lipitor trial where

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[3] CDC, *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*, at 3 (2014) (Ex. 11); *accord* Gale Rpt. (Ex. 12) at 9.

[4] *See, e.g.*, Gale Tr. (Ex. 1) at 77:15-78:7; Quon Tr. (Ex. 2) at 292:14-17; Roberts Tr. (Ex. 9) at 73:22-74:4; Wells Tr. (Ex. 13) at 80:16-81:10.

diabetes ***was*** a pre-specified endpoint, and which did not report a statistically significant association with diabetes. When this cherry-picking was noted at his initial deposition, Dr. Jewell responded by serving a "rebuttal" report on ASCOT. Yet this new report led him only into further error, as he contorted the ASCOT data to make it say that Lipitor ***significantly increases*** the risk of diabetes – the opposite of the researchers' actual, peer-reviewed finding. "If you torture the data long enough, it will confess to anything,"[5] and drawing inferences opposite those of the study authors is a methodology that courts reject as unreliable.

Plaintiffs' other experts' opinions are also methodologically flawed. They all rely on Dr. Jewell's deficient analysis of Lipitor clinical trials. They also cite interim data from a clinical trial abstract of the PROVE-IT trial, comparing Lipitor to Pravachol (pravastatin); the JUPITER clinical trial that compares Crestor (rosuvastatin) to placebo; and observational studies of Lipitor and other statins. None of these studies is a reliable basis for their opinions. The unpublished interim PROVE-IT abstract, which reported increased blood glucose with Lipitor compared to pravastatin, is meaningless in light of the final study data, published in a peer-reviewed journal, that reported no significant difference in the diagnosis of diabetes between the two groups. Plaintiffs' experts also rely on JUPITER, which reported a small increased risk of physician reports of diabetes with Crestor, but they ignore the many limitations of that finding, including reporting bias that distorted the fact that glucose levels were not significantly different in the two groups. Nor can Plaintiffs establish general causation based on observational studies, which, as nearly every one of Plaintiffs' experts admit, are subject to significant methodological limitations including chance, bias, and confounding, and can thus only generate hypotheses, not test them. Indeed, these experts admit that observational studies serve only hypothesis-generating purposes and are, thus, incapable of demonstrating causation.

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[5] These words are attributed to Professor Ronald Coase (1910-2013), a British economist and Nobel laureate. *See* https://www.coase.org/coasecv.htm. This maxim has been applied to statistical analyses. McShane, *Statistical Challenges in the Development and Evaluation of Marker-Based Clinical Tests*, 10 BMC Medicine 52 (2012) (Ex. 15) at 3.

**High (80 mg) Dose and Multiple Risk Factors for Diabetes**

To establish general causation, Plaintiffs must demonstrate not only that Lipitor causes diabetes, but at what dose it can do so. Plaintiffs' causation analysis stands largely on *post hoc* analysis of data from the SPARCL trial. That analysis, if accepted, reports only a small increase in the diagnosis of diabetes at the high 80 mg dose ***and*** only in patients with three or four preexisting risk factors for the disease: baseline fasting blood glucose above 100 mg/dl, fasting triglycerides above 150 mg/dl, BMI above 30, or a history of hypertension. Plaintiffs' experts recognize the importance of dosage in evaluating causation, but they fail to overcome the lack of reliable evidence of a valid association – let alone causation – at 10, 20, and 40 mg doses. The clinical trial data for Lipitor, including those from ASCOT at 10 mg that Dr. Jewell initially ignored, do not report a statistically significant association with increased diabetes diagnoses at any dose other than at 80 mg as reported in SPARCL. In fact, a published 2013 network meta-analysis of Lipitor trials by Navarese, which includes data from SPARCL, ASCOT, and other Lipitor clinical trials, shows no statistically significant increase at any dose. Further, findings from observational studies do not support Plaintiffs' experts' causation opinions because, as several of them admit and as noted above, due to their many limitations, observational studies are at best hypothesis generating. Other courts have precluded general causation testimony for lower dosages of a medicine where reliable evidence was absent. Not only do Plaintiffs' experts fail to analyze the data based on dose, but they also fail to make any showing as to duration, or whether an elevated risk of newly diagnosed diabetes occurs in patients who do not otherwise have multiple risk factors for being diagnosed with diabetes. Thus, at minimum, the Court should hold that Plaintiffs' experts cannot testify that Lipitor causes diabetes for those who took 10, 20, or 40 mg doses or for those who have less than three of the foregoing risk factors.

## BACKGROUND

### A. Diabetes Is a Progressive Disease That Takes 10 Years or More To Develop

"Diabetes is a group of metabolic diseases characterized by hyperglycemia," *i.e.*, elevated blood glucose, that affects the way the body metabolizes sugar, and which results from

progressive changes in the body's resistance to, or production of, insulin.[6] Diabetes "is a chronic and progressive condition," Elasy Rpt. (Ex. 17) at 7, which is diagnosed by measuring blood glucose levels.[7] These measurements are surrogate endpoints for the underlying disease process. *Id.* at 6. Under current American Diabetes Association (ADA) diagnostic criteria, a fasting blood sugar level less than 100 mg/dl is normal, 100 to 125 mg/dl is prediabetic, and above 126 mg/dl on two separate tests is diabetic. *E.g.*, *id.* at 6-7; Fonseca Rpt. (Ex. 18) at 4.

Diabetes is a slow, progressive disease. Dr. Quon describes the diabetes disease process: "[D]iabetes is a chronic disease and you start out with a little bit of insulin resistance. Then it gets more. Then you have impaired fasting glucose and then you have, you know, metabolic syndrome, and then you get frank diabetes. So there's a continuum." Quon Tr. (Ex. 2) at 53:23-54:20. "Even though 'new onset' diabetes is a term that is used in the literature to reflect newly diagnosed diabetes, the term is not medically accurate in the description of the disease process because diabetes is a long-term progressive disease that takes many years to develop." Miller Rpt. (Ex. 19) at 12; *see* Elasy Rpt. (Ex. 17) at 13-14.

Drs. Gale and Singh also admit the generally accepted scientific proposition that the time it takes someone to progress from normal, to prediabetic, to diabetic, is a period not just of years, but at least a decade. Dr. Gale admits that the progression from disease initiation until diagnosis is "a long, slow process" that takes "***at least a decade*** or so." Gale Tr. (Ex. 1) at 174:5-175:18; 183:6-12 (emphasis added). A diagnosis of diabetes is "not a new injury" but rather a "milestone" in a progressive disease process. *Id.* at 184:1-8. So, too, Dr. Singh agrees that the "[d]iabetes disease process does not start on that day of diagnosis" but "occurs over a continuum, you know, of time and age and risk factors." Singh Tr. (Ex. 3) at 62:10-25.[8]

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[6] ADA, *Diagnosis & Classification of Diabetes Mellitus*, 37 Diabetes Care S81, S81 & S82 (Fig. 1) (2014) (Ex. 16).

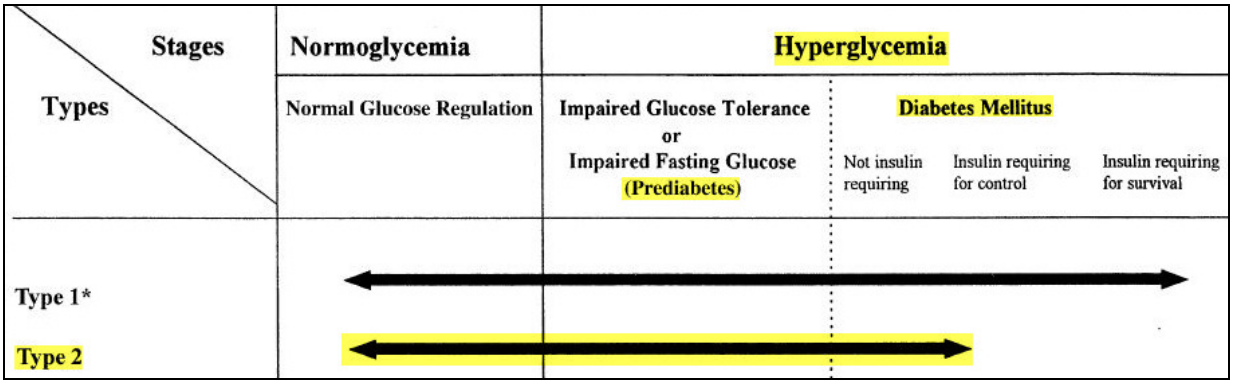
[7] Under more recent methods, glycated hemoglobin (HbA1c) levels in the fasting patient's blood can also be used to diagnose diabetes.

[8] Dr. Abramson also agrees that diabetes is a long-term process, but defers to a diabetes expert as to its length. Abramson Tr. (Ex. 4) at 180:4-182:3. Dr. Roberts, a cardiologist, offers little in the way of an opinion regarding diabetes, admitting that she is "not familiar with

Pfizer's experts also agree that the "[m]etabolic and cellular abnormalities (such as insulin resistance) related to the future development of diabetes often precede the diagnosis by at least 10-15 years," Fonseca Rpt. (Ex. 18) at 3, and that "[d]iabetes is a disease process, and diagnosis of diabetes is the end ('milestone') of the decade-long process of its development." Elasy Reb. Rpt. (Ex. 20) at 8; *see also* Miller Rpt. (Ex. 19) at 11-12.

Each of these stages is part of the disease process. As the ADA explains, "[a] disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes."[9] "One should not confuse the timing of disease diagnosis with the timing of disease onset – the disease onset occurs much earlier than its eventual diagnosis." Elasy Rpt. (Ex. 17) at 5.

The ADA has depicted the continuum of the diabetes disease process as follows:[10]




Plaintiffs' experts Drs. Quon and Gale admit that the "cut points" for diagnosing diabetes are somewhat arbitrary, have changed over time, and do not necessarily signify the occurrence of any clinically significant physiological change in one's vascular condition, but are diagnostic tools that can be used to treat patients and improve their health. *See* Quon Tr. (Ex. 2) at 73:19-

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the [ADA]" and does not "know what the [ADA] guidelines say," having not "read them." Roberts Tr. (Ex. 9) at 257:15-25, 175:10-16. She was thus unable to answer questions regarding the diabetic process, *id.* at 248:16-22, the existence of prediabetes (*id.* at 250:9-251:20), and whether diabetes process is "a continuum." *Id.* at 254:6-8.

[9] ADA (2014) (Ex. 16) at S81.

[10] *Id.* at S82, Fig. 1 (emphasis added).

24; 245:25-246:15. Dr. Gale explains that the cutoff between healthy glucose and harmful glucose needing intervention is "very difficult to define." Gale Tr. (Ex. 1) at 110:18-22; *see id.* at 137:18-24, 139:9-20. Yet "a number has to be picked out of the air" for clinical purposes to justify treatment. *Id.* at 43:17-44:11; 37:11-40:17. These diagnostic cut points should not be viewed, in binary terms, as a simple "'on' switch" where normal blood glucose ends and diabetes begins. *Id.* at 143:17-144:3. There is "no biological cutoff for the diagnosis of diabetes." *Id.* at 36:21-37:10. Under the term long used in the medical community, including by Pfizer's experts and employees, when one's blood glucose level crosses the cut point from prediabetes to diabetes, she will be labeled diagnostically as having "new onset diabetes." But the thing that is new about "new onset diabetes" is the diagnosis, not the progressive disease process.

Because "the cut-off levels that separate those with diabetes from those without are arbitrarily defined,"[11] there is little if any physiological significance to just crossing the threshold. As Dr. Gale testified, if a person's blood glucose goes from 124 mg/dl to 127 mg/dl, she may be diagnosed with diabetes, but "the person has not suddenly changed category or haven't gone green or anything, they're the same person with a slightly higher blood glucose." Gale Tr. (Ex. 1) at 42:11-43:16; *see* Quon Tr. (Ex. 2) at 249:7-252:7. Although what makes a diabetes diagnosis is high glucose values, "[w]hat makes diabetes mellitus a disease is the (vascular) complications that are the result from (chronically) high glucose values."[12]

In proffering their opinions, Plaintiffs' experts are focusing on very tiny increases in blood glucose that do not have clinical consequences. Dr. Gale estimates the increase as 0.1% in HbA1c – or about 2 to 3 mg/dl – which, on average "is not going to matter" and "would not worry [him] as a clinician." Gale Tr. (Ex. 1) at 49:12-50:1, 154:2-9, 205:2-13. Dr. Quon similarly agrees that such small changes are not "clinically relevant." Quon Tr. (Ex. 2) at 175:22-176:20. At most, small clinically insignificant glucose elevations occur in some people

[11] Gale, *Diagnosis & Classification of Diabetes Mellitus*, Diapedia.org (last modified August 29, 2014), at 3 (Ex. 21).

[12] *Id.* at 2.

who are already on the road to diabetes who may then be diagnosed with diabetes a bit sooner. *See* Gale Tr. (Ex. 1) at 208:13-209:2; Quon Tr. (Ex. 2) at 53:23-54:20. Moreover, Drs. Gale and Singh admit there is no evidence that Lipitor increases the risk of microvascular disease and complications. Singh Tr. (Ex. 3) at 71:8-12; Gale Tr. (Ex. 1) at 46:8-13. Indeed, Dr. Quon states that Lipitor can help protect against vascular disease. Quon Tr. (Ex. 2) at 70:17-71:20.

**B. Diabetes Is a Disease With Multiple Risk Factors, Including Age and Weight Gain**

In published literature, Plaintiffs' expert, Dr. Gale, concedes that diabetes is a "multifactorial" disease, for which the "causal mechanisms … remain unknown."[13] Dr. Gale admits that the risk of diabetes "is largely determined by the quartet of age, obesity, family history, and ethnicity," Gale Tr. (Ex. 1) at 133:18-23, with age and obesity being the "two main drivers." Gale Rpt. (Ex. 12) at 4; *accord* Gale Tr. (Ex. 1) at 134:6-14; Fonseca Rpt. (Ex. 18) at 10; Elasy Rpt. (Ex. 17) at 7; Miller Rpt. (Ex. 19) at 13. Other recognized conditions associated with diabetes include sedentary lifestyle, high blood pressure, high triglycerides, low high-density lipoprotein (HDL) cholesterol, depression, psychosis, cigarette smoking, and exposure to some environmental toxins. *See* Quon Tr. (Ex. 2) at 85:10-21; Fonseca Rpt. (Ex. 18) at 6; Elasy Rpt. (Ex. 17) at 7.

Given the multifactorial nature of the disease with other large and well-recognized risk factors and the slight alleged risk of Lipitor, none of Plaintiffs' experts is "aware of any method where you could say in an individual patient by how much Lipitor had an effect on or accelerated their diagnosis of diabetes." Gale Tr. (Ex. 1) at 209:17-210:2. Dr. Gale admits that the question of specific causation – whether Lipitor did cause diabetes in any particular person – is a "difficult issue" for Plaintiffs. *Id.* at 57:18-58:17. Dr. Quon has never told a patient that his or her diabetes was caused by a statin and has never seen a patient who he believed would not have gotten diabetes absent a statin. Quon Tr. (Ex. 2) at 326:18-327:4. Dr. Singh concedes that where "a patient stops taking Lipitor and the diabetes doesn't subside," it "[w]ould be fair to

[13] Gale, *Is type 2 diabetes a category error?*, 381 Lancet 1956, 1956 (2013) (Ex. 22).

infer that we cannot distinguish whether the diabetes is driven by Lipitor or other factors." Singh Tr. (Ex. 3) at 324:6-325:6. Dr. Abramson knows of no "test or procedure or method to make [the] determination" that Lipitor caused diabetes "in individual patients." Abramson Tr. (Ex. 4) at 161:6-25. As Dr. Gale admits, it is not "possible to determine whether or not [a patient] still would have developed diabetes had she not taken Lipitor." Gale Tr. (Ex. 1) at 210:14-19. Attempting to separate out one or two causes in an individual "really resists detailed dissection," *id.* at 79:15-80:4, and given the "very complex network of interrelationships within the body ... any attempt at dissection which takes one individual part on its own is going to fall short." *Id.* at 78:16-79:14.

Dr. Gale admits that the small increase in risk associated with statins pales in comparison to other well-recognized risk factors. For example, Dr. Gale admits that obesity is a far greater diabetes risk, Gale Tr. (Ex. 1) at 116:6-16; 178:4-15, and even "night shift work," which disrupts biorhythms, is a stronger risk factor than statins. *Id.* at 176:12-177:6. Pfizer's expert, Dr. Hennekens, explains that "[t]he reported magnitude of association between Lipitor and newly diagnosed diabetes, even if real, is small" and is overwhelmed by the large increased risk of diabetes arising from weight gain. Hennekens Rpt. (Ex. 14) at 51. Even "small increases in body weight from teenage years to adulthood confer[] alarming risks of type 2 diabetes" and for "a woman who has gained ***even a few pounds since age 16***, … her risk of developing diabetes due to that weight gain is ***much greater*** than what has been postulated about any statin in developing diabetes." Hennekens Tr. (Ex. 23) at 29:22-30:10, 157:2-19 (emphasis added).

It is beyond dispute that there is a diabetes epidemic in the United States. The CDC estimates that 9.3% of the U.S. population, or 29.1 million Americans, has diabetes.[14] Of those, 27.8% of the people with diabetes, or 8.1 million Americans, are undiagnosed.[15] Prediabetes, which afflicts some 86 million adults nationwide,[16] confers a substantially increased risk of

[14] CDC, *National Diabetes Statistics Report* (2014) (Ex. 11), at 1.
[15] *Id.*
[16] *Id.* at 3.

developing diabetes, Gale Rpt. (Ex. 12) at 9-10; Gale Tr. (Ex. 1) at 178:24-180:20, and this risk also far exceeds the alleged risk attributable to statins.[17] Because the same disease process can cause prediabetes and diabetes, and because individuals with prediabetes have a relatively high risk for being diagnosed with diabetes in the future,[18] there is no way to reliably rule out prediabetes as the cause of the individual's diabetes.

**C. Lipitor Clinical Trial History**

FDA approved the New Drug Application (NDA) for Lipitor in 1996. The NDA included safety and efficacy data from more than 21 clinical trials. Both Pfizer and FDA conducted analyses of the NDA safety data, including adverse event reports submitted by investigators during clinical trials and laboratory measurements collected during the trials. Based on these analyses, "hyperglycemia" was included in the original Lipitor labeling as an adverse reaction reported in clinical trials, without regard to causation. As shown above, "hyperglycemia" is a medical term that includes both "prediabetes" and "diabetes."[19]

Since its approval, Lipitor has been studied in many large, cardiovascular outcome-based clinical trials, the gold standard in testing. The Collaborative Atorvastatin Diabetes Study (CARDS) was a placebo-controlled trial designed to determine Lipitor's efficacy in patients with type 2 diabetes and risk factors for cardiovascular disease.[20] CARDS reported that Lipitor "significantly reduced the rate of major cardiovascular events" in this population "with a relative risk reduction of 37%." 2015 Lipitor Label (Ex. 5) at 17-18. Lipitor was thus approved to "[r]educe the risk of MI and stroke in patients with type 2 diabetes" and risk factors for heart disease. *Id.* at 1. CARDS did not report that Lipitor worsened or aggravated existing diabetes.

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[17] ADA, *Classification & Diagnosis of Diabetes*, 38 Diabetes Care (Supp. 1) S8, at S8-S16 (2015) (Ex. 24).

[18] ADA (2014) (Ex. 16) at S81, S85.

[19] *Id.* at S82, Fig. 1.

[20] Colhoun et al., *Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial*, 364 Lancet 685 (2004) (Ex. 25).

The Anglo-Scandinavian Cardiovascular Outcomes Trial (ASCOT) was a placebo-controlled trial designed to test Lipitor's efficacy in primary prevention – that is, preventing cardiovascular events in persons who had not experienced such an event.[21] ASCOT reported "a relative risk reduction of 36% … regardless of age, smoking status, obesity, or presence of renal dysfunction," 2015 Lipitor Label (Ex. 5) at 16-17, leading to Lipitor's approval for primary prevention. ASCOT also included diabetes as a pre-specified tertiary endpoint and was designed to contemporaneously collect and adjudicate diabetes data by a blinded endpoints committee. The results of this independent adjudication did not report a statistically significant association with diabetes (RR 1.15, 95% CI 0.91–1.44).[22] The study was consistent with a finding of no effect of Lipitor on diabetes diagnosis rates.

In addition to placebo-controlled trials, active comparator clinical trials were conducted. The IDEAL study compared high-dose Lipitor to Zocor (simvastatin) in patients with CHD. IDEAL reported a significant reduction in the "risk of other composite secondary end points and nonfatal acute [myocardial infarction]."[23] The Treating to New Targets (TNT) trial compared a 10 mg dose of Lipitor to the 80 mg dose in patients with CHD and reported that the 80 mg dose "significantly reduced the rate" of major cardiovascular events in the study population, "with a relative risk reduction of 22%." 2015 Lipitor Label (Ex. 5) at 18. Based on the results from TNT and IDEAL, FDA approved Lipitor for secondary prevention of CHD.

The Stroke Prevention through Aggressive Cholesterol Lowering (SPARCL) trial was a placebo-controlled trial designed to test whether 80 mg Lipitor prevents stroke in patients who

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[21] Sever et al., *Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial*, 361 Lancet 1149, 1150 (2003) (Ex. 26).

[22] *Id.* at 1153 tbl.3. "RR" denotes the relative risk, and "95% CI" denotes the 95% confidence interval, which are explained more thoroughly below.

[23] Pedersen et al., *High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial*, 294 JAMA 2437 (2005) (Ex. 27).

already had a stroke.[24] While diabetes was not an endpoint in SPARCL, Pfizer conducted a *post hoc* analysis, which it reported to FDA in 2007, of more physician reports of diabetes in the Lipitor group than placebo. This led to the following disclosure being added to the Lipitor label in 2009: "Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the [Lipitor] group and 89 subjects (3.8%) in the placebo group." 2015 Lipitor Label (Ex. 5) at 9.

Around the time of that label change, a group of investigators including Pfizer employees conducted another *post hoc* analysis of the SPARCL data as to diabetes. This exploratory analysis, published in 2011 together with analyses of TNT and IDEAL, reported that Lipitor 80 mg was "associated with a slightly increased risk" of newly diagnosed (*i.e.*, new onset) diabetes in SPARCL participants who already had risk factors for diabetes (RR 1.37, 95% CI 1.08-1.75).[25] Only patients with 3 or 4 preexisting risk factors for diabetes – including elevated glucose at baseline and high BMI – experienced an increased risk and only at 80 mg.[26] The analysis also reported that the strongest predictors of the new diagnosis of diabetes in these trials did not involve the use of statins, but rather "baseline fasting glucose level" and other risk factors for diabetes, "specifically higher triglycerides, higher BMI, and hypertension."[27] As one of its co-authors explained, "the study does not say that Lipitor causes diabetes." DeMicco Tr. (Ex. 30) at 607:24-609:7. Where there are no risk factors – or, indeed, less than three risk factors – there is no increased risk. The study found "no difference between Lipitor 80 and the comparator group" for zero to two risk factors, and a statistically significant association only in a "small number of patients who have three or four risk factors," and at the 80 mg dose. *Id.*

In 2012, as one of several so-called "class" changes to labeling for many different statins, FDA directed that the following language be added to the warnings section of the physician-

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[24] Amarenco et al., *High-Dose Atorvastatin after Stroke or Transient Ischemic Attack*, 355 NEJM 549 (2006) (Ex. 28).

[25] Waters et al., *Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials*, 57 J. Am. Coll. Cardiol. 1535, 1535 (2011) (Ex. 29).

[26] *Id.* at 1542.

[27] *Id.*

directed prescribing information for Lipitor: "Increases in HbA1c and fasting serum glucose levels have been reported with [statins], including LIPITOR." 2015 Lipitor Label (Ex. 5) at 6. This labeling change was instituted for Lipitor and several other statins based on FDA's review of various published statin studies and meta-analyses involving diabetes and glucose data. FDA emphasized that it "continues to believe that the cardiovascular benefits of statins outweigh these small increased risks."[28] FDA has never concluded that Lipitor causes diabetes.

**THRESHOLD SCRUTINY OF EXPERT TESTIMONY**

Throughout its threshold analysis, "the trial judge must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 589 (1993). These "exacting standards of reliability," *Weisgram v. Marley Co.*, 528 U.S. 440, 455 (2000), provide that "conjecture, hypothesis, subjective belief, or unsupported speculation are impermissible grounds on which to base an expert opinion." *Wehling v. Sandoz Pharm. Corp.*, 162 F.3d 1158, 1998 WL 546097, at *5 (4th Cir. 1998) (per curiam). Courts must ensure the expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999); *see Braun v. Lorillard Inc.*, 84 F.3d 230, 234 (7th Cir. 1996); *Watkins v. Telsmith, Inc.*, 121 F.3d 984, 990 (5th Cir. 1997); *Allen v. Pa. Eng'g Co.*, 102 F.3d 194, 198 (5th Cir. 1996). "[C]lose judicial analysis of expert testimony is necessary 'because expert witnesses are not necessarily always unbiased scientists.'" *Nelson v. Tenn. Gas Pipeline Co.,* 243 F.3d 244, 252 (6th Cir. 2001) (quoting *Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1352 (6th Cir. 1992)). "[T]he courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996).

Courts must exclude expert evidence that is not "based on sufficient facts or data," that is not "the product of reliable principles and methods," or that has not "reliably applied the

[28] FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs (Feb. 28, 2012) (Ex. 31).

principles and methods to the facts of the case." Fed. R. Evid. 702. "***[A]ny*** step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible. This is true whether the step completely changes a reliable methodology or merely misapplies that methodology." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994).

Though *Daubert* addresses methods, "[a]s the Supreme Court has recognized, 'conclusions and methodology are not entirely distinct from one another,'" *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 202 (4th Cir. 2001) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)), and the difference "has only limited practical import." *Paoli*, 35 F.3d at 746. "When a judge disagrees with the conclusions of an expert, it will generally be because he or she thinks that there is a mistake at some step in the investigative or reasoning process of that expert." *Id.* "[T]rial judges may evaluate the data offered to support an expert's bottom-line opinions to determine if that data provides adequate support to mark the expert's testimony as reliable." *Brown v. Nucor Corp.*, 785 F.3d 895, 936 (4th Cir. 2015) (quotation omitted). "A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered" and preclude the testimony. *Joiner*, 522 U.S. at 146.

While the *Daubert* inquiry is "a flexible one," there are general factors for determining reliability. *Daubert*, 509 U.S. at 593-94. Of particular importance is whether "the theory ... can be (and has been) tested." *Id.* at 593. Another factor is whether the theory has been subjected to evaluation by peer review and publication. *Id.* A third factor is the known or potential rate of error and the existence and maintenance of standards controlling the technique's operation. *Id.* at 594. A final consideration is whether the theory has been generally accepted in the scientific community. *Id.* These factors are "neither definitive nor exhaustive, however, and some factors may be more pertinent than others depending on the nature of the issue, the expert's particular expertise, and the subject of his testimony." *Newman v. Motorola, Inc.*, 218 F. Supp. 2d 769, 773 (D. Md. 2002) (quotation omitted), *aff'd*, 78 F. App'x 292 (4th Cir. 2003).

"'[E]xpert evidence can be both powerful and quite misleading.'" *Daubert*, 509 U.S. at 595 (citation omitted). Plaintiffs, as the proponents of the expert evidence, bear the burden of

showing that it is admissible. *In re Digitek Prods. Liab. Litig.*, 821 F. Supp. 2d 822, 837 (S.D.W.Va. 2011). Pfizer does ***not*** bear the burden of demonstrating its inadmissibility. *See Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 534 (W.D. Pa. 2003).

*Daubert* carefully distinguishes between the threshold reliability inquiry that Plaintiffs must satisfy and the role of cross-examination. "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky ***but admissible*** evidence .... These conventional devices ... are the appropriate safeguards ***where*** the basis of scientific testimony ***meets the standards*** of Rule 702." *Daubert*, 509 U.S. at 596 (emphasis added) (citations omitted). "[B]ut the testimony proffered here is not merely shaky: it is unreliable" and "should not be admitted." *Am. Honda Motor Co., Inc. v. Allen*, 600 F.3d 813, 818-19 (7th Cir. 2010).

**THE ELEMENTS OF GENERAL CAUSATION ARE ABSENT HERE**

"[T]o carry the burden of proving a plaintiff's injury was caused by exposure to a specified substance, the plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally as well as plaintiff's actual level of exposure." *Zellers v. NexTech Ne., LLC*, 533 F. App'x 192, 196 (4th Cir. 2013) (quotation omitted). "These two levels of causation are known as 'general causation' and 'specific causation.'" *Id.* at 196 n.6.

To establish general causation in a pharmaceutical products liability case, "the generally accepted method" begins, but does not end, by "look[ing] for statistically significant associations between medication exposure and [the injury], which are consistent and replicated across epidemiological studies." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 455 (E.D. Pa. 2014). "Statistical significance" is a measurement of the likelihood that any observed association – the relative risk or the odds ratio – is due to chance. Typically, this is a 95% likelihood that the true value lies within a range – the confidence interval – reported by the study. *Reference Manual on Scientific Evidence* (3d ed. 2011) (*RM* (3d)) at 579-81. Thus, if the confidence interval includes 1.0, which is known as the "null," the result is not statistically significant. *Id.*

A reliable methodology also considers whether any statistically significant result reflects a "true" association or a "false" association stemming from bias or confounding. *See id.* at 583-96. Bias refers to systematic, non-random error – for example, information bias where the available records for one group are more likely to include relevant information than another. *Id.* at 585. Confounding refers to related factors that may be the true or contributory cause of an observed association – for example, if the group taking the study medication has risk factors that may also be the cause of the disease being studied. *Id.* at 591.

If – and only if – a statistically significant true association is established through multiple studies, reliable methodology will then apply the Bradford Hill factors for evaluating whether the association is causal. *See Frischhertz v. Smithkline Beecham Corp.*, 2012 WL 6697124, at *3 (E.D. La. Dec. 21, 2012); *accord Dunn v. Sandoz Pharm. Corp.*, 275 F. Supp. 2d 672 (M.D.N.C. 2003). These factors include "strength of relationship, consistency, specificity, temporality, dose response, biologic plausibility, coherence, experimental evidence, and analogy." *Dunn*, 275 F. Supp. 2d at 677 n.5 (citing Sir Austin Bradford Hill, *The Environment and Disease: Association or Causation*, 58 Proc. Royal Soc'y Med. 295, 295-300 (1965) (Ex. 32)).

Plaintiffs' experts cannot satisfy the above standards. The clinical features of diabetes preclude them from establishing that anyone diagnosed with diabetes while on Lipitor would not have developed diabetes without Lipitor. They use unreliable methodology that ignores clinical understanding of diabetes in favor of a litigation-driven analysis, cherry-pick data to support their conclusions, and torture data to say the opposite of the study authors' conclusions. They have no evidence from clinical trials of a statistically significant association with new diagnoses of diabetes at doses less than 80 mg with people who have less than three risk factors for diabetes. This Court should exclude Plaintiffs' general causation opinions.

## I. PLAINTIFFS' EXPERTS CONTRADICT THEIR OWN CLINICAL WORK

### A. Plaintiffs' Experts' Causation Opinions Contradict Their Clinical Opinions

Plaintiffs' experts' general causation testimony is inadmissible. They offer litigation opinions that are contradictory to their experts' clinical opinions in their professional practice

regarding the diabetes disease process. While Plaintiffs' medical experts offer many opinions on the diabetes disease process, their causation opinions are based principally on the analysis of certain Lipitor clinical trial data by Dr. Jewell. Dr. Jewell is not a medical doctor or an epidemiologist, but a statistician. He has no experience in clinical practice and he refuses to address any clinical issues. Due to his lack of clinical knowledge or expertise, his causation opinion is untethered – and, in fact, contradictory – to the opinions of Plaintiffs' medical experts as to the diabetes disease process. Yet those experts nevertheless rely on Dr. Jewell's analysis without making any attempt to reconcile their litigation opinions with their own clinical understanding of the diabetes disease process based on their professional work. Plaintiffs' general causation opinions are thus unreliable and inadmissible.

**1. Plaintiffs' Experts Ignore Their Admissions on Diabetes Disease Progression**

The progression from diabetes disease initiation to diagnosis is, as noted, "a long, slow process" that takes "at least a decade or so." Gale Tr. (Ex. 1) at 174:5-175:18, 183:6-12; Quon Tr. (Ex. 2) at 240:3-24. Plaintiffs' expert testimony on the actual effect of Lipitor shows that they do not in fact think that Lipitor causes diabetes. For instance, Dr. Quon does not believe that statins initiate the diabetes disease process, Quon Tr. (Ex. 2) 82:18-83:23, but that Lipitor could "unmask" preexisting diabetes. *Id.* at 273:13-15. Likewise, Dr. Gale believes that Lipitor is "the straw that breaks the camel's back" and is "the final trigger that precipitates ... a clinical diagnosis" – but with a disease process that unfolds for many years before a patient reaches a blood glucose level that crosses the diagnostic threshold. Gale Tr. (Ex. 1) at 135:4-136:13. Apart from the problem of contending that "a contributing factor as figuratively insubstantial as a straw equates to a ***substantial*** contributing factor," *Haller v. AstraZeneca Pharms. LP*, 598 F. Supp. 2d 1271, 1299 (M.D. Fla. 2009), this testimony effectively concedes that the disease process begins many years before and, thus, is not caused by Lipitor.

"'[I]f a disease or illness in an individual preceded the established period of exposure, then it cannot be concluded that the chemical caused the disease.'" *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1243 (11th Cir. 2005) (quotation omitted). "Without exposure before the

disease, causation cannot exist." *RM* (3d) at 601. "[T]he exposure … must not just precede the outcome, but must do so by a period of time that is consistent with biologic mechanisms," for "[a] disease process that precedes the exposure cannot be caused by that exposure." Hennekens Rpt. (Ex. 14) at 31. As the Eleventh Circuit explained in a case alleging that a medicine caused diabetes, "[t]emporal proximity is generally not a reliable indicator of a causal relationship," particularly where "the development of diabetes occurs gradually over many years," but is diagnosed shortly after ingesting the alleged cause. *Guinn v. AstraZeneca Pharms. LP*, 602 F.3d 1245, 1254 (11th Cir. 2010). As Pfizer's expert Dr. Hennekens explains, "[s]ince diabetes develops over years to decades, the disease process is most likely to have begun well in advance of the initiation of statin therapy." Hennekens Rpt. (Ex. 14) at 55. Thus, whatever the studies that Dr. Jewell analyzed show, they cannot show that Lipitor causes pre-existing disease.

Dr. Jewell did not even attempt to square his statistical analysis with clinical medicine. In fact, he insisted he is unqualified to do so, stating repeatedly that he is "not a clinician." Jewell Tr. (Ex. 7) at 18:10-13, 33:18-22, 60:25-61:2, 95:16-96:4, 293:13-19. With no medical training, Dr. Jewell testified that he is not an expert in diabetes, *id.* at 18:5-6, not an expert in glucose metabolism, *id.* at 18:7-9, and not an expert in the diagnosis and development of clinical diseases. *Id.* at 61:24-62:6. He would not answer the questions of what level of fasting blood glucose physicians consider normal, *id.* at 18:25-19:7, how long it takes a person to develop Type 2 diabetes, *id.* at 61:11-14, or even what is Type 2 diabetes. *Id.* at 61:3-5. Yet he nevertheless considers himself qualified to develop a methodology for analyzing data concerning the diagnosis of diabetes in a host of clinical trials. Dr. Jewell's ignorance and disregard of the clinical features of the diabetes disease process renders his analysis unreliable.

While Plaintiffs' experts place less emphasis on Dr. Singh's analysis, it suffers from the same problem as Dr. Jewell's. Unlike Dr. Jewell, Dr. Singh is a medical doctor and purports to offer opinions on the clinical nature of diabetes. Yet his attempt to reconcile that clinical understanding with his analysis is circular and unreliable. *See O'Conner v. Commonwealth Edison Co.*, 807 F. Supp. 1376, 1396 (C.D. Ill. 1992), *aff'd*, 13 F.3d 1090 (7th Cir. 1994). Dr.

Singh recognizes the slow development of diabetes, stating that "[f]or the most part," diabetes takes place "over many years." Singh Tr. (Ex. 3) at 63:1-10. Yet he asserts that this was "[n]ot [true] for Lipitor" because "[i]n some of the statin studies it's occurring over four months" or "six months." *Id.* Dr. Singh thus assumes what he purports to prove: that Lipitor must be causing diabetes. Rather than conforming his opinions to the clinical fact of a slowly developing diabetes disease process, Dr. Singh distorts the facts to fit his theory. As a result, he unreliably assumes that the diabetes disease process occurs a full decade faster with Lipitor than under any other known circumstance. The law instructs that an expert cannot engage in circular reasoning and assume the very fact he has been engaged to resolve, *Clark v. Takata Corp.*, 192 F.3d 750, 757 (7th Cir. 1999), and this analytical leap renders Dr. Singh's opinion inadmissible.

Dr. Singh similarly opines that temporality supports causation because "[i]n each case, statin exposure occurred before the development of diabetes, and in the majority of cases, the onset of diabetes was relatively shortly after statin exposure (frequently < 4 months)." Singh Rpt. (Ex. 6) at 36. But the emphasis by Plaintiffs' experts on any association with new ***diagnosis*** of diabetes misses the point. By focusing on the diagnosis rather than the disease, Plaintiffs confuse the map with the terrain. A diagnosis of diabetes is like crossing the equator, an imaginary line with little geologic significance. Because diabetes takes "at least a decade or so" to develop, Gale Tr. (Ex. 1) at 174:5-175:18; 183:6-12; *see* Quon Tr. (Ex. 2) at 240:3-24, Plaintiffs' experts' focus should not be on the events immediately preceding the crossing of an arbitrary line, but the events that started the patient down the road to that line or materially moved her forward on it. Their failure to do so renders their testimony unreliable.

**2. Plaintiffs' Experts Ignore the Small Size of the Alleged Risk**

Plaintiffs' experts make much of the small alleged risk of newly-diagnosed diabetes associated with statin use, but they do little to explain the basis for their opinion that such a slight association is causal. The magnitude of a reported association is a key factor in assessing causality. *See Dunn*, 275 F. Supp. 2d at 677 n.5; Hill (1965) (Ex. 32) at 295-300. Here, Plaintiffs' experts' estimate of the risk is small. That alleged risk must be evaluated in the

context of other well recognized and far larger risks, some of which are more than 200 times larger. The risk of diabetes is, as Dr. Gale admits, "largely determined by the quartet of age, obesity, family history, and ethnicity." Gale Tr. (Ex. 1) at 133:18-23. Other recognized risk factors include sedentary lifestyle, high blood pressure, high triglycerides, low HDL cholesterol, depression, psychosis, cigarette smoking, and exposure to some environmental toxins. *See* Quon Tr. (Ex. 2) at 85:10-21; Fonseca Rpt. (Ex. 18) at 6; Elasy Rpt. (Ex. 17) at 7.

As Dr. Gale admits, the alleged risk associated with statins pales in comparison to the large relative risk conferred by increased weight. Gale Tr. (Ex. 1) at 116:6-16; 178:4-15. For example, compared to women with a BMI of less than 22, the relative risk of diabetes is 210% for women with a BMI of 22-22.9; 350% with a BMI of 23-23.9; and greater than 500% with a BMI of 25-26.9.[29] Hennekens Rpt. (Ex. 14) at 51-52. To put these BMIs in context, a BMI of 25-29 is considered overweight; obesity begins with a BMI of 30. In contrast, Dr. Singh states that, based on his own meta-analysis, the relative risk of diabetes attributable to statins is only about 9%. Singh Rpt. (Ex. 6) at 34. The risk allegedly associated with statins is further dwarfed by the presence of prediabetes, which is both a component of the same disease process and a risk factor that increases the risk of diabetes diagnosis as much as 2000% (or 222 times the risk that Dr. Singh attributes to statins).[30]

Because diabetes involves so many risk factors, none of Plaintiffs' experts is "aware of any method where you could say in an individual patient by how much Lipitor had an effect on or accelerated their diagnosis of diabetes." Gale Tr. (Ex. 1) at 209:17-210:2; *see also* Quon Tr. (Ex. 2) at 326:18-327:4; Singh Tr. (Ex. 3) at 324:6-325:6; Abramson Tr. (Ex. 4) at 161:6-25. As Dr. Hennekens explains, "it is difficult, if not impossible, to reliably detect any possible small hazards on diabetes which occur over a few years, in the context of proven large hazards such as

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[29] Body Mass Index (BMI) is "a person's weight in kilograms divided by the square of height in meters" and is "used to screen for weight categories." CDC, Body Mass Index, http://www.cdc.gov/healthyweight/assessing/bmi/.

[30] ADA (2015) (Ex. 24) at S10.

body weight and other major risk factors, which occur over decades." Hennekens Rpt. (Ex. 14) at 52. Nor do the clinical trials report a relative risk of diabetes greater than 2.0, which is a factor that some courts consider on the issue of specific causation. *RM* (3d) at 612.

Though the failure of Plaintiffs to reliably determine whether a given agent may have caused an individual Plaintiff's injury is typically a question of specific causation, here, because of the large number of well-recognized risk factors for diabetes, many of which exceed by several multiples the risk that Plaintiffs' experts attribute to Lipitor, there is a need to consider these issues generally. While Pfizer will be filing its specific causation *Daubert* motions in the near future, in this unique situation, the ability of Plaintiffs' experts to prove specific causation is thus relevant to the background of the Court's consideration of general causation as well. And if no expert can, using appropriate scientific methods, reliably opine which of a given set of risk factors caused diabetes in most if not all cases, then no expert can reliably opine as to causation. That Plaintiffs' experts purport to do so renders their testimony unreliable.

While Plaintiffs' position is that Lipitor causes diabetes, they cannot resort to the fall-back position of trying to claim causation of glucose elevation, rather than the diabetes disease process itself. This is so because the blood glucose elevations that they claim are associated with Lipitor, like the alleged risk of diabetes, are also very small and of no clinical significance. Plaintiffs' experts base their causation opinions on slight elevations of glucose, which, even if they cross a diagnostic threshold, do not necessarily signify any clinically significant physiological change. *See* Quon Tr. (Ex. 2) at 245:25-246:15; Gale Tr. (Ex. 1) at 143:17-144:3. Dr. Gale estimates the average glucose increase as 0.1% HbA1c – or 2 to 3 mg/dl – which on average "is not going to matter" and "would not worry [him] as a clinician." Gale Tr. (Ex. 1) at 49:12-50:1, 205:2-13, 154:2-9. Dr. Quon also agrees that such small changes are not "clinically relevant." Quon Tr. (Ex. 2) at 175:22-176:20. Thus, even if Plaintiffs try to narrow their experts' position to causation of increased glucose levels, such very small changes have no clinical effect. Plaintiffs' experts offer no evidence or scientific methodology to conclude that an admittedly clinically insignificant and minuscule elevation in blood glucose – raising HbA1c

by only 0.1% – is somehow causal or a substantial contributing factor to a decade long disease process that they admit is driven by multiple factors, age and obesity being "the two main drivers." Gale Rpt. (Ex. 12) at 4. This is a far cry from causing diabetes.

**3. Plaintiffs' Experts Concede There Is No Biological Plausibility**

Not only are Plaintiffs' causation opinions inconsistent with the admitted clinical course of diabetes, but Plaintiffs' clinical experts also concede that biological plausibility is not satisfied in this case. Singh Tr. (Ex. 3) at 363:11-364:24; *see also* Quon Tr. (Ex. 2) at 87:2-8; Gale Tr. (Ex. 1) at 68:13-69:14, 70:1-24. Some courts have excluded experts who, among other things, were unable to "describe the mechanism … that would cause [plaintiff's] condition." *Zellers v. NexTech Northeast, LLC*, 895 F. Supp. 2d 734, 747 (E.D. Va. 2012), *aff'd*, 533 F. App'x 192 (4th Cir. 2013); *accord Dellinger v. Pfizer Inc.*, 2006 WL 2057654, at *9 (W.D.N.C. July 19, 2006). Exclusion has thus been affirmed where the experts "were unable to explain the physiological mechanism" by which the substance at issue allegedly caused the disease. *Hollander v. Sandoz Pharms. Corp.*, 289 F.3d 1193 (10th Cir. 2002); *accord McClain*, 401 F.3d at 1245-46. The "inability to show a mechanism" – that is, a "testable biologic explanation" – "demonstrates a faulty methodology that is not scientifically valid." *Soldo*, 244 F. Supp. 2d at 571-72; *see also Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1361-62 (N.D. Ga. 2001). Plaintiffs lack any reliable methodology to explain how Lipitor causes diabetes within the known clinical pathways of the disease, which reinforces that Plaintiffs have "not shown that the experts' general-causation opinions are admissible." *DeGidio v. Centocor Ortho Biotech, Inc.*, 3 F. Supp. 3d 674, 687-88 (N.D. Ohio 2014).

**B. Dr. Jewell Creates a Litigation-Only Definition of "Glucose Abnormalities"**

The mismatch of statistical results and medical facts is not a glitch, but a feature, of Dr. Jewell's analysis. The error pervades his opinion through his definition of being "without baseline glucose abnormalities," which he created for purposes of this litigation and without any reference to generally accepted medical or clinical understanding. Dr. Jewell clung to his opinions throughout his deposition only by repeatedly disclaiming all clinical knowledge, even

as to the key assumptions driving his analysis. For example, he denied knowing how long it takes a person to develop Type 2 diabetes, Jewell Tr. (Ex. 7) at 61:11-19, whether the diabetes process is a continuum, *id.* at 63:6-12, and whether diabetes can exist in a patient and go undiagnosed for years. *Id.* at 66:13-16. The result is an analysis that is untethered to any meaningful medical understanding of diabetes.

This disregard of recognized scientific and medical knowledge is built into the foundation of Dr. Jewell's analysis. He creates his own, private definition of whether study subjects were "without baseline glucose abnormalities" when they entered the study – if their "baseline glucose" was ***less than or equal to 125 mg/dl***. Jewell Rpt. (Ex. 10) at 4 n.1. As Dr. Gale so gently puts it, Dr. Jewell "used a slightly unusual way" of defining the criteria for diabetes. Gale Tr. (Ex. 1) at 267:16-19. While it does not itself show a basic math error, through this definition, Dr. Jewell ignores prediabetic individuals with glucose values ***between 100 and 125 mg/dl***, who are nevertheless subject to the same disease process as those who pass the 125 mg/dl diagnostic cut point for diabetes. Dr. Jewell admits that he does not "talk about the term 'prediabetes' … anywhere in [his] report," Jewell Tr. (Ex. 7) at 71:8-13, he does not discuss whether prediabetes is a glucose abnormality, *id.* at 71:14-20, and he did not know or try to determine how many prediabetic individuals were in the studies he analyzed. *Id.* at 253:9-22; 283:12-19; 284:16-23; 285:20-286:12.

A statistician cannot take blood level ranges medically recognized as abnormal and redefine them as normal. Doing so "'reveals a methodological flaw that cannot be overlooked by the court'" and "[s]uch a definition of abnormality would deprive the term of all meaning." *Adams v. Cooper Indus., Inc.*, 2007 WL 1805586, at *4 (E.D. Ky. June 21, 2007) (quoting *Allgood v. General Motors Corp.*, 2006 WL 2669337, at *28-29 (S.D. Ind. Sept. 18, 2006)). It "is not a scientifically valid methodology because it does not take into account the normal distribution of data within a population." *Id.* For example, in *Adams*, the court noted that, under the expert's "approach, one would expect half the world's population of approximately six billion people (everyone with levels above the median) to be entitled to a

special medical monitoring program." *Id.* (quoting *Allgood*). The CDC estimates that some 86 million adults nationwide have prediabetes.[31] Gale Rpt. (Ex. 12) at 9. Deeming such people to be "without baseline glucose abnormalities," Jewell Rpt. (Ex. 10) at 4, n.1, cannot help but skew the meaning of Dr. Jewell's analysis. By waving his statistical wand, Dr. Jewell's definition renders millions of people "without baseline glucose abnormalities," contravening generally accepted medical knowledge.

Dr. Jewell claims that he ignored prediabetic individuals "for the sake of brevity" and just divided his analysis into two groups – those with and those (supposedly) "without baseline glucose abnormalities." Jewell Rpt. (Ex. 10) at 4 n.1; Jewell Tr. (Ex. 7) at 72:11-73:8. But reliability, not brevity, is the touchstone of the *Daubert* analysis. What Dr. Jewell treats as a binary distinction is instead acknowledged both by Plaintiffs' clinical experts and major public health organizations as an intermediate stage in the development of diabetes.

Though Dr. Jewell cites ADA materials that explain that prediabetes is part of the same disease process as diabetes, Dr. Jewell chooses to ignore that information. In the same ADA document about diabetes that Dr. Jewell cites, Jewell Rpt. (Ex. 10) at 25 n.55, the ADA explains that "[a] disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes." That is, there is "an intermediate group of individuals whose glucose levels do not meet criteria for diabetes, yet are higher than those considered normal. These people were defined as having impaired fasting glucose (IFG) [fasting plasma glucose (FPG) levels 100 mg/dl to 125 mg/dl]. [Such individuals] have been referred to as having prediabetes, indicating the relatively high risk for the future development of diabetes" and their IFG "can be observed as intermediate stages in" the development of Type 2 diabetes.[32]

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[31] CDC, National Diabetes Statistics Report (2014) (Ex. 11), at 3.
[32] ADA (2014) (Ex. 16) at S81 & S82 (Fig. 1).

Dr. Jewell protests that he "did not cite this paragraph at all in my report," and tries to justify his omission by making the startling assertion that "[i]t's not what I cited this document for." Jewell Tr. (Ex. 7) at 349:21-350:15. Dr. Jewell cannot simply cherry-pick favored propositions from the generally accepted sources he cites, especially where those sources undermine his analysis. Though Dr. Jewell testified that "it's quite clear [patients] are without a baseline glucose abnormality if – normally if they're less than or equal to 125 milligrams per deciliter," *id.* at 71:21-72:7, the generally accepted scientific view is decidedly the opposite. Dr. Jewell's testimony has previously been excluded due to offering clinical opinions beyond his expertise. *See In re Guidant Corp. Implantable Defibrillators Prods. Liab. Litig.*, 2007 WL 1964337, at *11 (D. Minn. June 29, 2007). Here, as well, his testimony should be stricken because he simply ignores recognized, well-accepted medical knowledge.

**C. Dr. Jewell's Litigation-Only Opinions Are a Moving Target**

Plaintiffs sought to cure the error of Dr. Jewell's litigation-only definition of "without baseline glucose abnormalities" with revised opinions after Dr. Jewell's initial deposition. Belatedly recognizing this error, Dr. Abramson served an errata at his deposition disclaiming his previous reliance on Dr. Jewell's definition. Abramson Errata (Ex. 33). That is, when the problem with this definition "was brought to Dr. Jewell's attention in his deposition," Dr. Abramson "thought that was a fair comment on Pfizer's part." Abramson Tr. (Ex. 4) at 150:2-17. Since his and Dr. Jewell's use of "the term 'baseline glucose abnormality' to describe people whose blood sugar was above 125 was the wrong term," he wanted to correct it. *Id.* at 178:1-12. In reality, a "baseline glucose abnormality" is "anything over 100." *Id.* at 179:22-180:3. Similarly, Dr. Jewell served a "rebuttal" report that purports to stratify his SPARCL analysis according to various glucose thresholds. Jewell Reb. Rpt. (Ex. 34) at 32-34.

But rather than saving their opinions, the evolution of these experts' opinions in response to these challenges shows that their methods are not based on science, but are designed for litigation. Courts have properly excluded such expert evidence where it was a "veritable moving target" whose "underpinnings … have changed in direct response" to litigation scrutiny.

*Haller*, 598 F. Supp. 2d at 1296-97; *see also Miller v. Pfizer, Inc.*, 356 F.3d 1326, 1330 (10th Cir. 2004); *Glastetter v. Novartis Pharms. Corp.*, 107 F. Supp. 2d 1015, 1032 (E.D. Mo. 2000), *aff'd*, 252 F.3d 986 (8th Cir. 2001). In *Bausch & Lomb*, Judge Norton rejected similar expert testimony that was "in flux throughout [the] litigation," and subject to change through a "supplemental report … containing additional opinions." *In re Bausch & Lomb, Inc. Contact Lens Solution Prods. Liab. Litig.*, 2009 WL 2750462, at *12 (D.S.C. Aug. 26, 2009). An expert's "willingness to abandon or qualify her opinions when faced with further facts, undermines the reliability of her opinions." *Id.* at *13. So, too, here.

## II. PLAINTIFFS' GENERAL CAUSATION METHODOLOGY IS UNRELIABLE

### A. Plaintiffs' Experts Conflate Association With Causation

Plaintiffs' experts' general causation opinions are unreliable because they are predicated on a fatal – and elementary – conflation of association with causation. With regard to his analysis of SPARCL, Dr. Jewell testified that his opinion that SPARCL showed "significantly increased risk of new onset diabetes with 80 milligrams of [Lipitor] ... means that Lipitor causes [new onset diabetes] as defined in SPARCL." Jewell Tr. (Ex. 7) at 93:9-94:6. Dr. Abramson made the same error, testifying that the terms "causation" and "association" are "used interchangeably," and "it's semantics." Abramson Tr. (Ex. 8) at 483:18-488:16. But as a fundamental scientific principle, "it should be emphasized that an association is ***not equivalent to causation***." *RM* (3d) at 552 (emphasis added); *Miller v. Pfizer, Inc.*, 196 F. Supp. 2d 1062, 1079-80 (D. Kan. 2002); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 591 (D.N.J. 2002). "Any scientist or statistician must acknowledge, … correlation is not causation." *Huss v. Gayden*, 571 F.3d 442, 459 (5th Cir. 2009). As Dr. Roberts testified, "[t]he two are not synonymous." Roberts Tr. (Ex. 9) at 83:17-22.

Dr. Jewell purported to justify his elimination of the distinction between association and causation by erroneously asserting that "there is no other explanation" than causation for an observed association "in a randomized trial." Jewell Tr. (Ex. 7) at 94:7-16. There are other explanations for significant findings in randomized trials. Even a statistically significant result

cannot avoid the possibility of mere chance, which can only be avoided through replication in multiple studies. The likelihood of a statistically significant but false result increases when an expert like Dr. Jewell goes beyond study hypotheses and conclusions and instead conducts a *post hoc* search for associations within study data. *RM* (3d) at 577 n.82. "When researchers examine many possible associations that might exist in their data – known as data dredging – we should expect that even if there are no true causal relationships, those researchers will find statistically significant associations in 1 of every 20 associations examined." *Id.*

As Dr. Hennekens explains, "simply because the results of an individual randomized trial not designed *a priori* to test the hypothesis, exclude chance … does not necessarily imply the presence of a valid statistical association, let alone a judgment of causality." Hennekens Rpt. (Ex. 14) at 74. "Causality … is a judgment that is made on the totality of evidence, not from the results of a single randomized trial, and only after applying a number of positive criteria as originally described by Bradford Hill." *Id.* at 73. Here, the randomized clinical trials on statins report "inconsistent results in directionality, magnitude, and significance." Hennekens Rpt. (Ex. 14) at 41. Further, adverse events in clinical trials may also be subject to reporting bias when they are based on physician or patient reports, rather than objective criteria. Sacks Rpt. (Ex. 35) at 48-49. Even for a true association, reliable science must consider other factors, including the Bradford Hill factors of an appropriate temporal sequence and biological mechanism, to determine whether a valid association is causal. *Frischhertz v. Smithkline Beecham Corp.*, 2012 WL 6697124, at *3 (E.D. La. Dec. 21, 2012); *Dunn*, 275 F. Supp. 2d 678-80. Yet Dr. Jewell failed to do so here.

**B. Dr. Jewell's Opinion Is Based on Studies That Do Not Test His Hypothesis**

Dr. Jewell's causation opinion is also flawed because it is premised on a *post hoc* analysis of studies that were not designed to test whether Lipitor is associated with diabetes. As Dr. Jewell conceded, he initially "did not analyze any other data than the data coming from SPARCL, TNT, IDEAL and the NDA placebo controlled trial[s]." Jewell Tr. (Ex. 7) at 323:10-15. Yet he asserts that only one of these studies – SPARCL – is capable of showing causation,

since the NDA placebo-controlled studies were six months or less in duration and TNT and IDEAL involved active comparators, not placebo. Jewell Rpt. (Ex. 10) at 12, 48, 61; Jewell Tr. (Ex. 7) at 93:9-94:6.[33] But neither SPARCL nor any of these other studies were designed beforehand to test whether Lipitor is associated with diabetes.

"'Scientific' knowledge is generated through ... subjecting testable hypotheses to the crucible of experiment in an effort to disprove them." *United States v. Bynum*, 3 F.3d 769, 773 (4th Cir. 1993); *accord Black v. Rhone-Poulenc, Inc.*, 19 F. Supp. 2d 592, 598 (S.D.W.Va. 1998). Thus, "[e]pidemiologists use an analytic tool known as the 'null hypothesis,' which postulates that there is no association between a specific exposure and a particular outcome. ... The goal of an epidemiological study is to determine whether one can reject the null hypothesis and conclude that, in fact, there is an association between the exposure and the outcome." *Wade-Greaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1451-52 (D.V.I. 1994), *aff'd*, 1994 WL 16973481 (3d Cir. 1994); *accord Chambers v. Exxon Corp.*, 81 F. Supp. 2d 661, 665 (M.D. La. 2000), *aff'd*, 247 F.3d 240 (5th Cir. 2001). "[I]f the individual trials were not designed *a priori* to test the hypothesis, then a statistically significant association found in the meta-analysis should be considered hypothesis formulating, not testing." Hennekens Rpt. (Ex. 14) at 21.

Here, because the studies Dr. Jewell analyzed were not designed to study any association with diabetes or new diagnoses of diabetes, they were capable only of generating a hypothesis, not of testing it. Dr. Gale acknowledges this, stating that *post hoc* analyses such as those offered by Dr. Jewell "have to be handled with caution" because "methodological problems arise," and that they are "***hypothesis generating at best***." Gale Tr. (Ex. 1) at 270:11-271:7 (emphasis added). This is true of Dr. Jewell's analyses in general, as well as his sub-analysis of women. *See* Jewell Rpt. (Ex. 10) at 24. Because the trials on which Dr. Jewell relies were "not designed *a priori* to test the hypothesis that there is a valid statistical association between Lipitor and newly diagnosed diabetes, … chance, bias, and confounding remain plausible

[33] Beyond the inability of the NDA data to show causation, Plaintiffs' experts' analysis of that data is fatally flawed. *See* § IV.A of Pfizer's motion to exclude Dr. Abramson.

alternative explanations." Hennekens Rpt. (Ex. 14) at 6. "[I]t is not good scientific methodology to highlight certain elevated subgroups as significant findings without having earlier enunciated a hypothesis to look for or explain particular patterns." *Newman*, 218 F. Supp. 2d at 779. Yet that is what Dr. Jewell does with his *post hoc* analysis. It is therefore unreliable and inadmissible to establish causation.

**C. Dr. Jewell Cherry-Picks Data to Support His Litigation Opinion**

Not only did Dr. Jewell base his causation opinion on a single study, SPARCL, that was not designed to test his hypothesis, he simply ignored the studies that did not support his hypothesis – CARDS and ASCOT. Proper methodology requires the assessment of the totality of data to determine whether there are consistent, true associations reliably replicated in multiple studies. *See RM* (3d) at 604-05. But Dr. Jewell based his initial opinion on a single study, a method that Plaintiffs' other experts reject as unscientific. As Dr. Quon states, replication and consistency are important "[b]ecause you want to make sure that something [did not] happen by chance[,] that goes towards replicability" and "you want to make sure that ... the data is going the same way, you know, and in multiple independent trials that were designed robustly." Quon Tr. (Ex. 2) at 342:9-343:9. Dr. Quon also agrees that, rarely, if ever, does a single study conclusively demonstrate a cause-and-effect relationship. *Id.* at 344:24-345:2. Dr. Singh likewise concedes that where, as with diabetes, there is a significant background rate of the outcome in question, a single study does not conclusively demonstrate a cause-and-effect relationship. Singh Tr. (Ex. 3) at 353:5-12; *accord* Wei Rpt. (Ex. 36) at 12; Hennekens Rpt. (Ex. 14) at 73. Yet that is precisely what Dr. Jewell purports to do here.

Dr. Jewell admits that he did not review the CARDS study, Jewell Tr. (Ex. 7) at 132:22-133:3, which showed that Lipitor is effective in treating the vascular risk associated with diabetes, providing the basis for Lipitor's indication for primary prevention in persons with Type 2 diabetes. Even more glaring is Dr. Jewell's intentional decision "not to study the data in ASCOT" – a large, multi-year Lipitor trial in which diabetes ***was*** studied as a pre-specified

tertiary endpoint, and which showed no statistically significant association between Lipitor and diabetes. *Id.* at 119:5-15; *see also id.* at 121:24-122:3; 124:17-24; 125:14-22.

In other litigation, Dr. Jewell has criticized the methods he uses here, discounting other analyses for purportedly "fail[ing] to do a comprehensive review of the literature." Jewell *Foster* Tr. (Ex. 37) at 337:17-341:24. He criticized such analyses because they did not "have many of the studies that [he] relied on" and, thus, were "not really satisfactory as a report on the issue of [general causation]" and were "unacceptable … as a thorough investigation of the issue." *Id.* at 321:24-323:1, 331:25-332:22. He said he could not participate in an approach that "would take selectively saying, 'Well, we can keep [one study] in, but we … can't have [another study].'" *Id.* at 316:19-317:5. In contrast to his approach here, he said he "think[s] it's better to look at … the comprehensive review of the literature by a statistician if you are going to write a statistical report." *Id.* at 337:17-341:24; *accord* Sacks Reb. Rpt. (Ex. 38) at 14.

Despite having given such strong sworn testimony elsewhere, Dr. Jewell uses a different method here. In trying to defend his glaring omission of ASCOT, he says "[y]ou do not need to do a comprehensive review [of all relevant clinical trials] to answer the question that Lipitor causes diabetes in SPARCL, which is my opinions in this case and in this report." Jewell Tr. (Ex. 7) at 103:13-24. He also asserts that he did "not need to rely on other trials to necessarily inform me of what a specific trial says about the causal effects of Lipitor." *Id.* at 97:10-20. In sum, Dr. Jewell applies a double-standard, tailored to meet the demands of his assignment in a given case. As other courts have held in excluding expert testimony, such an omission "is especially glaring against [his] own deposition testimony that … '[a]ll evidence should be taken into account.'" *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004). Such "selectivity in defining the universe of relevant evidence thus violated his own standard of proper methodology …, which suggests that he does not apply the same rigor in the courtroom that he would apply to his [professional] endeavors." *Id.*

Courts have repeatedly rejected such "cherry-picking" of favorable data, which "does not reflect scientific knowledge, is not derived by the scientific method, and is not 'good science.'"

*In re Bextra & Celebrex Mktg. Sales Pracs. & Prods. Liab. Litig.*, 524 F. Supp. 2d 1166, 1176 (N.D. Cal. 2007). As the *Zoloft* MDL court recently held in excluding the plaintiffs' general causation evidence in its entirety, an expert who "selectively discuss[es] studies most supportive of her conclusions ... and fails to account adequately for contrary evidence" must be excluded, for "this methodology is not reliable or scientifically sound." *Zoloft*, 26 F. Supp. 3d at 460-61. There, the court rejected the general causation expert's testimony as unreliable where, like Dr. Jewell here, her "conclusions are drawn from trends she observed in a self-selected subset of supportive studies, not the totality of the epidemiological evidence." *Id.* at 461-62. "[A]ny theory that fails to explain information that otherwise would tend to cast doubt on that theory is inherently suspect," and courts have accordingly "excluded expert testimony 'where the expert selectively chose his support from the scientific landscape.'" *In re Rezulin Prod. Liab. Litig.*, 369 F. Supp. 2d 398, 425 & n.164 (S.D.N.Y. 2005) (citation omitted).

"Coming to a firm conclusion first and then doing research to support it is the antithesis of" a scientific method. *Claar v. Burlington N. R.R. Co.*, 29 F.3d 499, 502-03 (9th Cir. 1994). It is an "internally inconsistent" methodology, *Phillips v. Am. Honda Motor Co.*, 238 F. App'x 537, 541 (11th Cir. 2007), that is "contrived to reach a particular result." *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1293 n.7 (11th Cir. 2005). Where an expert "cherry-picked the facts he considered to render an expert opinion … such a selective use of facts fails to satisfy the scientific method and *Daubert*." *Barber v. United Airlines, Inc.*, 17 F. App'x 433, 437 (7th Cir. 2001); *see Fail-Safe, LLC v. A.O. Smith Corp.*, 744 F. Supp. 2d 870, 889 (E.D. Wis. 2010).

Dr. Jewell's methodology thus fails every one of the core *Daubert* guidelines. *Daubert*, 509 U.S. at 593-94. Rather than relying on a methodology that has been tested, he bases his causation opinion with respect to diabetes on a single study, SPARCL. Reliance on a single study is subject to a high rate of error. His analysis of SPARCL is unpublished and has not been subject to peer review. Nor is that approach generally accepted. "A plaintiff must present more than a single study showing correlation," and Dr. Jewell's attempt to stand on that ground alone is inadmissible. *Huss*, 571 F.3d at 459. His opinion must be excluded.

**D. Dr. Jewell Manipulates Study Data to Say What He Wants**

After Dr. Jewell was deposed over his failure to consider ASCOT, he tried to cure his omission with a supplemental report addressing ASCOT. Jewell Reb. Rpt. (Ex. 34) at 2-3. This supplemental analysis created more problems for Dr. Jewell than it solved.

ASCOT was designed to collect data on diabetes and to subject them to adjudication by a blinded endpoints committee. ASCOT did not find a statistically significant association with diabetes. Yet Dr. Jewell did not follow the report of the ASCOT study authors, but instead conducted his own *post hoc* analysis of the unadjudicated data. *See id.* at 9-18. As Dr. Gale admits, even if performed correctly, a *post hoc* analysis can only generate a hypothesis; it cannot be reliably used to test a hypothesis. Gale Tr. (Ex. 1) at 270:11-271:7; *accord* Wei Reb. Rpt. (Ex. 39) at 1. Dr. Jewell's reanalysis was not even performed correctly.

Among other flaws, Dr. Jewell's reanalysis did not use the adjudicated data from the ASCOT investigators, Jewell Tr. (Ex. 40) at 407:7-16, despite his admission that data reviewed by the blinded endpoint committee is "certainly more reliable than unadjudicated endpoint data" he used for his reanalysis. *Id.* at 447:19-449:12. Moreover, in his reanalysis, Dr. Jewell reached "conclusions the authors of the study do not make." *McClain*, 401 F.3d at 1248. In fact, he reaches precisely the opposite conclusions and, thus, "exceed[s] the limits of the conservative scientific methodology." *Id.* The ASCOT authors concluded that there was no statistically significant association between Lipitor and diabetes, a pre-specified endpoint in the analysis.[34] Dr. Jewell disregarded the study design and its conclusion, finding a statistically significant association between Lipitor and diabetes in ASCOT. Jewell Reb. Rpt. (Ex. 34) at 18. He has no scientifically valid reason for doing so.

An expert cannot base a causation opinion on studies that do not reach that conclusion. *Joiner*, 522 U.S. at 145-46. "It is axiomatic that causation testimony is inadmissible if an expert relies upon studies or publications, the authors of which were themselves unwilling to

[34] Sever (2003) (Ex. 26) at 1153, Tbl. 3.

conclude that causation had been proven." *Huss*, 571 F.3d at 459; *Happel v. Wal-Mart Stores, Inc.*, 602 F.3d 820, 826 (7th Cir. 2010); *Doe v. Ortho-Clinical Diagnostics, Inc.*, 440 F. Supp. 2d 465, 472-74 (M.D.N.C. 2006). "When an expert relies on the studies of others, he must not exceed the limitations the authors themselves place on the study" and "must not draw overreaching conclusions." *In re Accutane Prods. Liab. Litig.*, 511 F. Supp. 2d 1288, 1291 (M.D. Fla. 2007). The law "warns against use of medical literature to draw conclusions not drawn in the literature itself .... Reliance upon medical literature for conclusions not drawn therein is not an accepted scientific methodology." *Rutigliano v. Valley Bus. Forms*, 929 F. Supp. 779, 785 (D.N.J. 1996), *aff'd*, 118 F.3d 1577 (3d Cir. 1997). Dr. Jewell's unpublished, unreviewed reanalysis of ASCOT data to bolster his litigation opinion is unreliable and renders his testimony inadmissible.

In affirming the exclusion of expert testimony in *Joiner*, the Supreme Court held that a "study did not support the experts' conclusion" on causation where its authors were "unwilling to say that [the] exposure had caused" the disease in the population. 522 U.S. at 145. Similar issues were also before the Supreme Court in *Daubert*, where the plaintiffs' experts opined that a drug caused birth defects based, in part, upon "the 'reanalysis' of previously published epidemiological (human statistical) studies" – reanalyses that were "'unpublished, not subject to the normal peer review process and generated solely for use in litigation.'" 509 U.S. at 583-85. On remand, the Ninth Circuit noted that "[o]ne very significant fact to be considered is whether the experts … developed their opinions expressly for purposes of testifying." *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995). Yet the only "review" those opinions received was in the courtroom. *Id.* at 1318. As the court aptly noted, "what's going on here is not science at all, but litigation." *Id.* So, too, here.

In addition, Dr. Jewell used different methods for analyzing ASCOT. For SPARCL, IDEAL, and TNT, he initially performed analyses by gender, purporting to show that the risk of diabetes is greater in women than in men, *see* Jewell Rpt. (Ex. 10) at 4, 18, 27, 30, 31, 58, 70, a key allegation of Plaintiffs in this litigation. Yet, at his first deposition, Dr. Jewell conceded

that the ASCOT data, with a hazard ratio of 1.01 in women, suggested a lower risk in women than in men. Jewell Tr. (Ex. 7) at 128:17-129:6. Thus, using his approach in ASCOT would show "there is no evidence of an increased risk with" women. Wei Reb. Rpt. (Ex. 39) at 5. Now claiming that "the difference between men and women" is "not central to" his "original report" or to his "opinions," Jewell Tr. (Ex. 40) at 491:17-492:4, Dr. Jewell abandoned his gender analysis in ASCOT. *See* Jewell Reb. Rpt. (Ex. 34). That Dr. Jewell applies different methods to different studies demonstrates that he tailors his approach to the situation presented and underscores the unreliability of his *post hoc* reanalysis of the data.

Dr. Jewell's unpublished, non-peer-reviewed reanalysis is solely a litigation-driven, *post hoc* analysis designed to manipulate the data in a manner that ostensibly supports his preordained opinion. *See In re Denture Cream Prods. Liab. Litig.*, 2015 WL 392021, at *18 (S.D. Fla. Jan. 28, 2015). Dr. Jewell's reanalysis is "driven by h[is] desire to confirm h[is] *a priori* hypothesis" that Lipitor causes diabetes. *See Zoloft*, 26 F. Supp. 3d at 457 n.25. This is not science, but advocacy, and it has no place in the courtroom.

**E. Plaintiffs' Causation Opinions Based on Other Evidence Are Unreliable**

Though Plaintiffs' experts rely predominantly on the opinion of Dr. Jewell to support general causation, they also proffer a meta-analysis from Dr. Singh that purports to show that statins in general cause diabetes, Singh Rpt. (Ex. 6) at 7, 15-20, as well as their own causation opinions.[35] While Dr. Jewell's analysis is based on Lipitor clinical trial data, Plaintiffs' other experts opine that Lipitor causes diabetes based on the interim PROVE-IT abstract comparing Lipitor to pravastatin, the JUPITER trial comparing Crestor to placebo, and observational studies of Lipitor and other statins. Such studies cannot support causation here.

Plaintiffs' experts rely on an abstract reporting interim data from PROVE-IT, which reported a statistically significant increase in HbA1c levels in the Lipitor group, but they ignore the final published data for the study, which found no significant difference in the incidence of

[35] *See* Abramson Rpt. (Ex. 41) at 186-223; Gale Rpt. (Ex. 11) at 14-16; Quon Rpt. (Ex. 42) at 13-20; Roberts Rpt. (Ex. 43) at 8-13.

diabetes. Hennekens Rpt. (Ex. 14) at 72. Where an expert relies on unpublished findings and ignores the final report of a study, it suggests that their "reliance on the unpublished … report was not based on scientific method but on the expediencies of this particular litigation." *Rezulin*, 309 F. Supp. 2d at 562-63. Plaintiffs' experts likewise fail to note that PROVE-IT reported no elevated risk for the 80 mg dose of Lipitor compared to pravastatin. Based on data from the WOSCOPS trial, pravastatin was reported to have a ***protective*** effect against diabetes, *see* Singh Rpt. (Ex. 6) at 10, which raises serious questions about Plaintiffs' experts' hypotheses that they fail to address. And more fundamentally, PROVE-IT cannot establish general causation because it did not compare Lipitor to placebo, but to another active medication. Plaintiffs' experts' unscientific approach to this study is inadmissible.

Plaintiffs' experts attempt to establish general causation based on the JUPITER study of Crestor (rosuvastatin), *see, e.g.*, Singh Rpt. (Ex. 6) at 9-10, which was terminated after 1.9 years when Crestor had conclusively shown a benefit. Initially, Plaintiffs' experts engage in cherry-picking by relying on JUPITER, which reported a positive association with physician-reported diabetes (RR=1.25, 95% CI 1.05-1.49),[36] but ignoring statin studies with the opposite result – specifically, analysis of the data from WOSCOPS (Ex. 44), which reported a protective effect between pravastatin and diabetes. Moreover, Plaintiffs' experts ignore significant limitations of the JUPITER study that cast doubt on its finding. For instance, because JUPITER was terminated after 1.9 years due to proof of benefit, it is incapable of showing causation of a disease that takes a decade to develop, and "secondary endpoints [such as diabetes] are less reliable than if the trial had continued to its scheduled duration." Hennekens Rpt. (Ex. 14) at 40. Further, JUPITER did not use solely objective criteria to define diabetes, but instead included physician reports, which introduces a potential source of bias. *See* Sacks Rpt. (Ex. 35) at 49-50. The potential of bias is evident in the fact that the average glucose levels were

[36] Ridker et al., *Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial*, 380 Lancet 565 (2012) (Ex. 45).

actually identical between the two groups during the study period.[37] Any apparent showing that more Crestor patients developed diabetes in the JUPITER trial than those on placebo thus would have involved patients in whom the diabetes process had already begun. And finally, the reported association in JUPITER involved patients who already had risk factors for diabetes – as Dr. Singh admitted, neither SPARCL, nor JUPITER, nor any other statin clinical trial has reported a statistically significant increased risk of diabetes in patients without pre-existing risk factors for diabetes. Singh Tr. (Ex. 3) at 129:10-16; *accord* Hennekens Rpt. (Ex. 14) at 40.

Nor can Plaintiffs' experts rely on observational studies since, as many of them admit, such studies have substantial limitations and cannot show causation. As Dr. Quon admits, "observational studies are among the weakest type of evidence" and, rather than proving causation, they "form[] the basis for developing a hypothesis." Quon Tr. (Ex. 2) at 296:16-297:2; *accord* Sacks Rpt. (Ex. 35) at 57; Miller Rpt. (Ex. 19) at 10; Waikar Rpt. (Ex. 47) at 11-12. Dr. Gale agrees that "[i]n terms of establishing a causal relationship … [y]ou rely on your randomized controlled trials" because observational studies are hypothesis generating and "don't address the question of causation." Gale Tr. (Ex. 1) at 219:4-221:1. This is because in an observational study there can be more than 10 or 15 different potential confounders that would need to be adjusted for when assessing whether statins increase the risk of newly diagnosed diabetes, "which is why [Dr. Gale] ha[s]n't placed reliance on them for that." *Id.* at 222:7-15.[38] Many different confounders need to be accounted for when comparing a population of people taking statins to a population of people not taking statins, *id.* at 221:24-222:5, making "observational studies … notoriously easy to criticize." *Id.* at 223:5-16.

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[37] Ridker et al., *Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein*, 359 NEJM 2195 (2008) (Ex. 46).

[38] Of Plaintiffs' experts, only Dr. Roberts opines that observational studies present better data on diabetes than the randomized placebo controlled trials. Roberts Tr. (Ex. 9) at 110:17-111:2, 176:11-18. This notion is contrary to the widely accepted view that clinical trials are the "gold standard" of epidemiological evidence. *See RM* (3d) at 658.

These problems of confounding are multiplied when combined together as they are in Dr. Singh's meta-analysis of multiple sources of data, including observational studies, Lipitor clinical trials, and clinical trials for other statins. Dr. Singh agrees that when evaluating the relationship between statins and diabetes, a number of different confounders need to be taken into account, including age, obesity, high blood glucose, smoking, family history, hypertension, and lifestyle. Singh Tr. (Ex. 3) at 215:9-217:21. Yet Dr. Singh failed to adjust for confounding in comparing disparate data from multiple different studies and did not conduct any type of analysis to determine the degree to which his meta-analysis results were confounded by the failure to adjust for potential confounders. *Id.* at 289:24-290:14. Thus, Plaintiffs' other experts opinions on general causation must be excluded.

## III. PLAINTIFFS LACK RELIABLE EVIDENCE FOR DOSES UNDER 80 MG

In addition to the methodological problems outlined above, Plaintiffs' expert opinion on general causation fails to provide any information on the critical issue of dose. Under *Daubert*, it is not enough to claim that a substance is capable of causing injury at some unknown dose. "[A]ll chemical agents are intrinsically hazardous – whether they cause harm is only a question of dose. Even water, if consumed in large quantities, can be toxic." *RM* (3d) at 636; *see also In re W.R. Grace & Co.*, 355 B.R. 462, 486 n.99 (Bankr. D. Del. 2006). Dose is critical to proving general causation. "[T]o carry the burden of proving a plaintiff's injury was caused by exposure to a specified substance, the plaintiff must demonstrate the ***levels of exposure*** that are hazardous to human beings generally." *Zellers*, 533 F. App'x at 196 (emphasis added, quotation omitted); *accord Allen*, 102 F.3d at 199; *Abuan v. Gen. Elec. Co.*, 3 F.3d 329, 333 (9th Cir. 1993); *Mitchell v. Gencorp, Inc.,* 165 F.3d 778, 781 (10th Cir. 1999). Simply put, "dose matters," and the Court should "analyze plaintiffs' experts' opinions as to causation" on each specific dose as to which they allege harm. *Bextra & Celebrex*, 524 F. Supp. 2d at 1174-75.

For example, in *McClain*, the plaintiffs claimed that an appetite suppressant caused heart attacks and strokes. The district court denied the defendant's *Daubert* motion on general causation, but the Eleventh Circuit reversed, excluding the plaintiffs' experts because they could

offer no reliable testimony on what dose was necessary to cause injury. In other words, the experts "could not say how much is too much." 401 F.3d at 1241. "To carry the burden in a toxic tort case, 'a plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure to the defendant's toxic substance before he or she may recover.'" *Id.* (quoting *Mitchell*, 165 F.3d at 781). Because the plaintiffs failed to satisfy this requirement, the district court erred in admitting into evidence the experts' opinions that "use of [the product] actually causes strokes or heart attacks, either generally or in these Plaintiffs." *Id.* at 1255.

Several of Plaintiffs' experts assert that the risk of diabetes from Lipitor appears to be dose-dependent. Gale Tr. (Ex. 1) at 52:19-53:6; Quon Tr. (Ex. 2) at 48:19-49:13; Singh Rpt. (Ex. 6) at 36-37. Dr. Singh opines that "Lipitor causes diabetes" at all doses and "you cannot disaggregate the risk" by dose. Singh Tr. (Ex. 3) at 70:4-23. Yet Dr. Singh testified that, if asked to evaluate the effects of Lipitor at a given dose, it would be reasonable and appropriate to focus on the available data at a given dose, *id.* at 162:12-18, but nonetheless asserted that he had "to ascribe the risk to all doses" in his analysis. *Id.* at 268:9-23. In the end, none of these three experts, including Dr. Singh, attempted to analyze the effect of Lipitor by dose. Singh Tr. (Ex. 3) at 70:24-71:7; Gale Tr. (Ex. 1) at 54:7-55:3; Quon Tr. (Ex. 2) at 318:22-319:10.

Plaintiffs proffer no dose-specific evidence of an association with new diabetes diagnosis for any dose except 80 mg. In fact, no clinical trial reports any such association at a dose less than 80 mg. Gale Tr. (Ex. 1) at 252:19-253:1; Fonseca Rpt. (Ex. 18) at 19. Under the case law, the evidence, and their own admissions, Plaintiffs' general causation opinion on diabetes hangs on a *post hoc* analysis of SPARCL involving an 80 mg dose, in patients with preexisting risk factors for diabetes, such as elevated baseline glucose and high BMI.

Not only is there an absence of affirmative evidence of an association at any dose less than 80 mg, there is evidence to the contrary. ASCOT studied the 10 mg dose of Lipitor but found no statistically significant association with diabetes. Gale Tr. (Ex. 1) at 248:17-249:2. Plaintiffs cannot use Dr. Jewell's tortured *post hoc* reanalysis of ASCOT to turn its published

peer-reviewed results on their head. *See id.* at 270:11-271:7; *Happel*, 602 F.3d at 826; *Huss*, 571 F.3d at 459.

The ASCOT finding of no significant increased risk of newly diagnosed diabetes at 10 mg of Lipitor is also supported by a 2013 comprehensive network meta-analysis of randomized controlled trials by Navarese.[39] This network meta-analysis includes data from ASCOT, SPARCL, TNT, and IDEAL, and is the only published, peer-reviewed meta-analysis that provides risk estimates for specific doses of the major statins on the market. For Lipitor 10 mg, the risk of newly diagnosed diabetes was virtually identical to placebo, a finding consistent with no association. Drs. Gale and Singh admit that this meta-analysis did not find a significant increased risk of diabetes compared to placebo for the 10 mg dose – or the 80 mg dose – of Lipitor. Gale Tr. (Ex. 1) at 256:4-25; Singh Tr. (Ex. 3) at 191:25-192:19, 200:22-201:8. Dr. Singh admits that the Navarese meta-analysis was "quite reasonably well conducted," Singh Tr. (Ex. 3) at 191:20-24, and that he was aware of those data when he wrote his report, *id.* at 201:3-5, but did not address them. *Id.* at 200:8-15.

For the reasons outlined above, none of the other proffered clinical trials offers reliable evidence of causation at a lower dose. Dr. Jewell recognizes the limitations of the NDA data due to their short duration and does not contend that such data show causation. Jewell Rpt. (Ex. 10) at 3, 13. Dr. Singh claims that the NDA data established an increased risk of diabetes at 10 mg, but could not identify any of the NDA studies that allegedly show such a risk, and admits that he did not analyze the NDA data. Singh Tr. (Ex. 3) at 201:9-202:18, 313:18-316:5. Dr. Singh agrees that different doses of statins appear to have different diabetes risks. *Id.* at 268:9-23. He further agrees that it is reasonable and appropriate to focus on the data available at a given dose. *Id.* at 161:11-162:18. Yet neither he nor Dr. Quon made any effort to examine the data to determine what, if any, increased risk for diabetes diagnosis exists at 10 mg. *Id.* at 71:8-

[39] Navarese et al., *Meta-Analysis of Impact of Different Types and Doses of Statins on New-Onset Diabetes Mellitus*, 111 Am. J. of Cardiol. 1123, 1126-27, Fig. 3 (2013) (Ex. 48).

13; Quon Tr. (Ex 2) at 318:22-319:10. Nor do the active comparator trials such as TNT, IDEAL, and PROVE-IT establish an association at a lower dose. In addition to comparing Lipitor to placebo, the studied dose of Lipitor in each of these trials was 80 mg. While certain observational studies may report an association at 10 mg, Plaintiffs cannot rely on such "notoriously easy to criticize" studies, Gale Tr. (Ex. 1) at 223:5-16, which "don't address the question of causation." *Id.* at 219:4-220:14. Finally, JUPITER cannot answer questions on the dose of Lipitor because it involves a different medication.

Thus, even if Plaintiffs could proffer an admissible general causation opinion based on the data from SPARCL participants on the 80 mg dose of Lipitor (which they cannot), it would not provide evidence of general causation for any of the lower doses: 40 mg, 20 mg, or 10 mg. As Dr. Gale admits, SPARCL "by definition" does not provide any information about the effects of Lipitor on diabetes incidence at doses below 80 mg. Gale Tr. (Ex. 1) at 272:11-15. Other MDL courts have held in similar situations that a lack of such evidence warrants preclusion of general causation testimony at applicable doses. For instance, in the *Bextra & Celebrex* MDL, the court dismissed the plaintiffs' attempt to establish general causation for Celebrex at the 200 mg dose because, as here, their experts "rel[ied] on the handful [of studies] that appear to support their litigation-created opinion" and ignored the rest. 524 F. Supp. 2d at 1181. The court explained that, "[i]n the words of the Supreme Court, the 'analytical gap' between the data and these experts' conclusion is simply too great to make the opinion admissible," and therefore precluded all evidence of general causation at the 200 mg dose. *Id.* Likewise, the *Prempro* MDL rejected efforts to rely "on a study of a high dose to determine adverse effects of a lower dose, without supplying a method to substantiate this inference," which Plaintiffs' experts do not offer here. *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 895 (E.D. Ark. 2010) (citing *Bextra & Celebrex*, 524 F. Supp. 2d at 1180; *Soldo*, 244 F. Supp. 2d at 546-47). The same result is warranted here, and this Court should thus, at minimum, exclude Plaintiffs' general causation testimony for all doses less than 80 mg.

## IV. NO RELIABLE EVIDENCE FOR LESS THAN THREE RISK FACTORS

Even if one were to credit Dr. Jewell's analysis of an association with diabetes in SPARCL, it cannot support Plaintiffs' broad claim of causation in all patients at all doses for all durations. Dr. Jewell claimed to have framed his "analysis of the question of Lipitor in diabetes as outlined in the Waters report" and, thus, the "main protocol for doing [his analysis] was the Waters paper of trying to follow the studies they used and the methods they used." Jewell Tr. (Ex. 7) at 134:5-15, 370:21-371:5. Yet the increased risk of new diabetes diagnoses as assessed in Waters (2011) for SPARCL, TNT, and IDEAL was found only in patients (at the 80 mg dose) with three or four of the following risk factors for diabetes: baseline fasting blood glucose above 100 mg/dl, fasting triglycerides above 150 mg/dl, BMI above 30, or a history of hypertension.[40] In contrast, that analysis found no significant association for patients with zero to two risk factors. Despite Dr. Jewell's claim of having used the analysis and methods that Waters (2011) used, he freely admits that he did not assess the data by number of major risk factor for diabetes, including prediabetes, triglycerides, obesity, or hypertension. *Id.* at 257:11-259:17. Indeed, Plaintiffs' experts have not attempted to address this aspect of the Waters study in formulating their opinions. Thus, they lack reliable evidence of an association – let alone causation – in individuals with less than three of the foregoing risk factors.

## CONCLUSION

For the foregoing reasons, the Court should preclude Plaintiffs' experts, including Drs. Abramson, Gale, Jewell, Quon, Roberts, and Singh, from testifying that Lipitor causes diabetes. At minimum, the Court should preclude Plaintiffs' experts from testifying that Lipitor causes diabetes (a) at doses less than 80 mg or (b) in those with less than three of the following risk factors for diabetes: (i) baseline fasting blood glucose above 100 mg/dl, (ii) fasting triglycerides above 150 mg/dl, (iii) BMI above 30, or (iv) a history of hypertension.

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[40] Waters (2011) (Ex. 29) at 1540-42.

Dated: July 24, 2015

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I hereby certify that, this 24th day of July, 2015, I have electronically filed a copy of the above and foregoing with Clerk of the Court using the ECF system, which sent notification of such filing to counsel of record.

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## APPENDIX – General Causation Experts and Clinical Trials

**Plaintiff Experts:**

| | |
|---|---|
| **Name:** | John Abramson |
| **Employment:** | Primarily self-employed; Lecturer, Department of Health Care Policy, Harvard Medical School |
| **Certifications:** | Family Medicine |
| **Clinical Practice:** | Inactive since 2002 |
| **Education:** | M.D. (Brown University 1976); M.S. Family Medicine (Case Western Reserve University 1982) |
| **Reports:** | Opening Report (Ex. 41), Errata (Ex. 33), Rebuttal Report (Ex. 49) |

| | |
|---|---|
| **Name:** | Edwin Gale |
| **Employment:** | Emeritus Professor of Diabetic Medicine, University of Bristol |
| **Certifications:** | Diabetes (UK); General Medicine (UK) |
| **Clinical Practice:** | Inactive since 2011 |
| **Education:** | M.B. (University College Hospital, London, 1972); F.R.C.P. (UK 1982) |
| **Reports:** | Opening Report (Ex. 11) |

| | |
|---|---|
| **Name:** | Nicholas Jewell |
| **Employment:** | Professor of Biostatistics & Statistics, School of Public Health & Department of Statistics, University of California, Berkeley |
| **Certifications:** | N/A |
| **Clinical Practice:** | N/A |
| **Education:** | Ph.D. Mathematics (University of Edinburgh 1976) |
| **Reports:** | Opening Report (Ex. 9), Rebuttal Report (Ex. 34) |

| | |
|---|---|
| **Name:** | Michael Quon |
| **Employment:** | Professor, Department of Endocrinology, Diabetes, and Nutrition & Department of Physiology, University of Maryland School of Medicine |
| **Certifications:** | Internal Medicine |
| **Clinical Practice:** | Currently engages in treatment via clinical research; inactive in primary care since 1995 |
| **Education:** | Ph.D. Biomedical Engineering (Northwestern University 1987); M.D. (Northwestern University 1988) |
| **Reports:** | Opening Report (Ex. 42) |

| | |
|---|---|
| **Name:** | Barbara Roberts |
| **Employment:** | Associate Clinical Professor of Medicine, the Warren Alpert Medical School of Brown University; Director of the Women's Cardiac Center, Miriam Hospital |
| **Certifications:** | Internal Medicine; Cardiology |
| **Clinical Practice:** | Currently treats cardiology patients |
| **Education:** | M.D. (Case Western Reserve School of Medicine 1968) |
| **Reports:** | Opening Report (Ex. 43) |

| | |
|---|---|
| **Name:** | Sonal Singh |
| **Employment:** | Assistant Professor of Medicine, Division of General Internal Medicine, Department of Medicine & Department of Health, Policy and Management and International Health, Johns Hopkins University |
| **Certifications:** | Internal Medicine |
| **Clinical Practice:** | Currently treats primary care patients |
| **Education:** | M.B.B.S. (Patna Medical College, India 1998); M.P.H. (Bloomberg School of Public Health 2008) |
| **Reports:** | Opening Report (Ex. 6) |

**Pfizer Experts:**

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|---|---|
| **Name:** | Tom Elasy |
| **Employment:** | Chair of Clinical Research in the Diabetes Center & Associate Professor of Medicine, Vanderbilt University School of Medicine |
| **Certifications:** | Internal Medicine |
| **Clinical Practice:** | Currently treats and oversees treatment of patients with diabetes and prediabetes |
| **Education:** | M.D. (University of Maryland 1991); M.P.H. Epidemiology (University of North Carolina at Chapel Hill, School of Medicine 1998) |
| **Reports:** | Opening Report (Ex. 17), Rebuttal Report (Ex. 20) |

| | |
|---|---|
| **Name:** | Vivian Fonseca |
| **Employment:** | Professor of Medicine & Chief of the Section of Endocrinology, Tulane University Health Sciences Center |
| **Certifications:** | Internal Medicine, Diabetes, and Endocrinology (UK); Internal Medicine; Endocrinology, Metabolism, and Diabetes |
| **Clinical Practice:** | Currently treats patients with endocrine disorders, diabetes, and prediabetes |
| **Education:** | M.B.B.S. (Armed Forces Medical College, Poona, India 1947); M.D. (Bombay University 1978); F.R.C.P. (UK 2004) |
| **Reports:** | Opening Report (Ex. 18) |

| | |
|---|---|
| **Name:** | Charles Hennekens |
| **Employment:** | Professor & Senior Academic Advisor to the Dean & Research Professor, Charles E. Schmidt College of Medicine, Florida Atlantic University; Adjunct Professor of Family and Community Medicine, Meharry Medical College; Voluntary Professor, Department of Family Medicine and Community Health, University of Miami Miller School of Medicine |
| **Certifications:** | Preventive Medicine |
| **Clinical Practice:** | Inactive since 2000 |
| **Education:** | M.D. (Cornell University Medical College 1967); M.P.H. (Harvard School of Public Health 1973); M.S. Epidemiology (Harvard School of Public Health 1973); Dr.PH Epidemiology (Harvard School of Public Health 1975); honorary D.Sc. (University of Medicine and Dentistry of New Jersey 1996); honorary D.Sc. (Queens College, The City University of New York 1997) |
| **Reports:** | Opening Report (Ex. 23) |

| | |
|---|---|
| **Name:** | Michael Miller |
| **Employment:** | Professor of Cardiovascular Medicine, Epidemiology and Public Health, University of Maryland School of Medicine |
| **Certifications:** | Internal Medicine; Clinical Lipidology; Cardiovascular Disease |
| **Clinical Practice:** | Currently treats cardiology patients |
| **Education:** | M.D. (University of Medicine & Dentistry of New Jersey 1983) |
| **Reports:** | Opening Report (Ex. 19) |

| | |
|---|---|
| **Name:** | Frank Sacks |
| **Employment:** | Professor of Cardiovascular Disease Prevention, Department of Nutrition, Harvard School of Public Health; Professor of Medicine, Harvard Medical School; Senior Physician, Channing Division of Network Medicine, Department of Medicine, Brigham & Women's Hospital |
| **Certifications:** | N/A |
| **Clinical Practice:** | Inactive since 2010 |
| **Education:** | M.D. (Columbia University, College of Physicians and Surgeons 1977) |
| **Reports:** | Opening Report (Ex. 35), Rebuttal Report (Ex. 38) |

| | |
|---|---|
| **Name:** | Sushrut Waikar |
| **Employment:** | Associate Professor of Medicine, Harvard Medical School; Director of Ambulatory Services, Renal Division, Brigham and Women's Hospital |
| **Certifications:** | Internal Medicine; Nephrology |
| **Clinical Practice:** | Currently treats patients with diabetic kidney disease and other forms of acute and chronic kidney disease |
| **Education:** | M.D. (Yale University School of Medicine 1998); M.P.H. Clinical Effectiveness (Harvard School of Public Health, 2006) |
| **Reports:** | Opening Report (Ex. 47) |

| | |
|---|---|
| **Name:** | Lee-Jen Wei |
| **Employment:** | Professor of Biostatistics, Harvard University |
| **Certifications:** | N/A |
| **Clinical Practice:** | N/A |
| **Education:** | Ph.D. Statistics (University of Wisconsin, Madison) |
| **Reports:** | Opening Report (Ex. 36), Rebuttal Report (Ex. 39) |

**Chronological Listing of Relevant Clinical Trials**

| | |
|---|---|
| **Short Name & Date:** | WOSCOPS (1995) |
| **Full Name:** | West of Scotland Coronary Prevention Study |
| **Publication:** | Shepherd et al., *Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia,* 333 NEJM 1301 (1995) (Ex. 44) |
| **Study Drugs:** | Pravachol 40 mg vs. placebo |

| | |
|---|---|
| **Short Name & Date:** | ASCOT-LLA (2003) |
| **Full Name:** | Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm |
| **Publication:** | Sever et al., *Prevention of Coronary and Stroke Events with Atorvastatin in Hypertensive Patients who Have Average or Lower-than-Average Cholesterol Concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): A Multicentre Randomised Controlled Trial*, 361 Lancet 1149 (2003) (Ex. 26) |
| **Study Drugs:** | Lipitor 10 mg vs. placebo |

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|---|---|
| **Short Name & Date:** | CARDS (2004) |
| **Full Name:** | Collaborative Atorvastatin Diabetes Study |
| **Publication:** | Colhoun et al., *Primary Prevention of Cardiovascular Disease with Atorvastatin in Type 2 Diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre Randomised Placebo-Controlled Trial*, 364 Lancet 685 (2004) (Ex. 25) |
| **Study Drugs:** | Lipitor 10 mg vs. placebo |

| | |
|---|---|
| **Short Name & Date:** | PROVE–IT (2004) |
| **Full Name:** | Pravastatin or Atorvastatin Evaluation and Infection Therapy |
| **Publication:** | Cannon et al., *Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes*, 350 NEJM 1495 (2004) (Ex. 50) |
| **Study Drugs:** | Lipitor 80 mg vs. Pravachol 40 mg |

| | |
|---|---|
| **Short Name & Date:** | IDEAL (2005) |
| **Full Name:** | Incremental Decrease in End Points Through Aggressive Lipid Lowering |
| **Publication:** | Pedersen et al., *High-dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction: The IDEAL Study: a Randomized Controlled Trial*, 294 JAMA 2437 (2005) (Ex. 27) |
| **Study Drugs:** | Lipitor 80 mg vs. Zocor 20 mg |

| | |
|---|---|
| **Short Name & Date:** | TNT (2005) |
| **Full Name:** | Treating to New Targets |
| **Publication:** | LaRosa et al., *Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease*, 352 NEJM 1425 (2005) (Ex. 51) |
| **Study Drugs:** | Lipitor 80 mg vs. Lipitor 10 mg |

| | |
|---|---|
| **Short Name & Date:** | SPARCL (2006) |
| **Full Name:** | Stroke Prevention through Aggressive Cholesterol Lowering |
| **Publication:** | Amarenco et al., *High-Dose Atorvastatin after Stroke or Transient Ischemic Attack*, 355 NEJM 549 (2006) (Ex. 28) |
| **Study Drugs:** | Lipitor 80 mg vs. placebo |

| | |
|---|---|
| **Short Name & Date:** | JUPITER (2008) |
| **Full Name:** | Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin |
| **Publication:** | Ridker et al., *Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein*, 359 NEJM 2195 (2008) (Ex. 46) |
| **Study Drugs:** | Crestor 20 mg vs. placebo |